

PATENT

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NEW APPLICATION TRANSMITTAL

Transmitted herewith for filing is the patent application of: John R. CARLSON, Inventor(s):

Junhvong KIM, Peter J. CLYNE. Coral G. WARR,

NOVEL FAMILY OF ODORANT RECEPTORS IN DROSOPHILA For:

- This new application is for a: 1.
 - [Utility

[] Design

[] Plant

Papers enclosed which are required for a filing date: 2.

Pages of specification including

- 1 Title Page
- Pages of claims and
- Page(s) of Abstract 1 Sheets of
 - [] FORMAL

INFORMAL

drawings containing

29 Figures

> The enclosed drawing(s) are photograph(s), and there is also attached a [] PETITION TO ACCEPT PHOTOGRAPH(S) AS DRAWING(S)

Combined Declaration and Power of Attorney 3.

Enclosed - and is executed by all inventors

Not Enclosed

This application is being filed under the provisions of 37 C.F.R. §1.53(d). Applicant(s) await notification from the Patent and Trademark Office of the time set for filing the Declaration and paying the filing fees.

1.	Language				
		English			
	[]	Non-English			
		This application is being filed in accordance with 37 C.F.R. §1.52(d) and §608.01 of the MPEP. Applicant(s) await notification from the Patent and Trademark			
		Office of the time set for filing the verified English translation and the processing fee.			
5.	Assignment				
	11.	is attached and Assignment of the invention is to			
		also enclosed is the Form PTO 1595, Recordation Form Cover Sheet.			
	[]	will be filed at a later date			
6.		Certified Copy Application(s) from which priority is claimed are:			

Country		Application No. 60/117,132		Filed January 25, 1999	
United States					
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Certified copy(ies) is/are [] attached [] will follow

Fee Calculation

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	Number Filed	er Filed Number Extra a		Basic Fee Utility\$760.00 Design\$310.00
Total Claims (37 CFR 1.16(c))	- 20 =		\$ 18.00 each=	+
Independent Claims (37 CFR 1.16(b))	- 3 = \$ 78.00		\$ 78.00 each=	+
Multiple dependent claim	+			
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Reduction by 1/2 for filing by a small entity - \$				
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8.	Small	Entity Statement(s) Verified Statement(s) that this is a filing by a small entity under 37 C.F.R. §1.9 and §1.27 is(are) attached.			
9.	Fee Payment				
	[1]	Not Enclosed. NO FEE IS BEING PAID BY CHECK OR DEPOSIT ACCOUNT AT THIS TIME. This application is being filed under the provisions of 37 C.F.R. §1.53(d). Applicant(s) await notification from the Patent and Trademark Office of the time set for filing the Declaration and paying the filing fees.			
	[]	Enclosed. A check in the amount of \$ representing the filing fee of \$ and an assignment recording fee of \$ is enclosed. Except for issue fees payable under 37 C.F.R. §1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 CFR §1.16 and §1.17 which may be required, or credit any overpayment to Deposit Account 50-0310.			
10.	Additional papers enclosed.				
10.	[] [] [] [\blue]	Preliminary Amendment Information Disclosure Statement and Form PTO-1449 Citations Declaration of Biological Deposit Submission of "Sequence Listing", computer readable copy and/or amendment pertaining thereto for biotechnology invention containing nucleotide and/or amin acid sequence.			

Respectfully submitted,

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NOVEL ODORANT RECEPTORS IN DROSOPHILA

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5 RELATED APPLICATIONS

This application claims priority to U.S. provisional patent application Serial No. 60/117,132 filed January 25, 1999 which is herein incorporated by reference in its entirety.

10 U.S. GOVERNMENT SUPPORT

This work was supported by a grant from the National Institutes of Health (DC-02174).

FIELD OF THE INVENTION

This invention pertains to novel olfactory receptors and to methods of using such receptors. More particularly, this invention pertains to the nucleic acids and amino acids of novel olfactory receptors in *Drosophila* and to methods of using such nucleic acids and amino acids.

20 BACKGROUND OF THE INVENTION

Animals can detect a vast array of odors with remarkable sensitivity and discrimination. Olfactory information is first received by olfactory receptor neurons (olfactory receptors), which transmit signals into the central nervous system (CNS) where they are processed, ultimately leading to behavioral responses. An enormous amount of investigation into olfactory function, organization, and development has been carried out in insect model systems for many years (Kaissling et al., (1987) Ann. NY Acad. Sci. 510, 104-112; Hildebrand (1995) Proc. Natl. Acad. Sci. USA 92, 67-74). However, a number of central questions have been refractory to incisive analysis because the receptor

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molecules to which odor molecules bind have not been identified, in any insect.

To investigate the molecular mechanisms of olfactory function and development, applicants studied the olfactory system of *Drosophila melanogaster*, which is highly sensitive and capable of odor discrimination (Siddiqi, (1991) Olfaction in *Drosophila*, in: Wysocki & Kare (ed.), Chemical Senses, Marcel Dekker; Carlson (1996) Trends Genet. 12, 175-180). There are two olfactory organs on the adult fly, the third segment of the antenna and the maxillary palp (Figure 1A). In both organs, olfactory receptors are housed in sensory hairs called sensilla. The organization of the approximately 1200 olfactory receptors of the antenna is complex but ordered. On the antenna there are different morphological categories of sensilla: s. trichodea, s. coeloconica, large s. basiconica, and small s. basiconica (Figure 1B). The different morphological categories of sensilla are distributed in overlapping patterns across the surface of the antenna (Figures 1C-F) (Venkatesh & Singh, (1984) Int. J. Insect Morphol. Embryol. 13, 51-63; Stocker, (1994) Roux's Arch. Dev. Biol. 205, 62-72).

Electrophysiological studies show that each morphological category of sensilla can be divided into different functional types (denoted by different colors in Figures 1C-F), defined by the characteristic response profiles of their olfactory receptors (Rodrigues et al., (1991) Mol. Gen. Genet. 226, 265-276; Clyne et al., (1997) Invert. Neurosci. 3, 127-135; de Bruyne et al., unpublished results). For s. trichodea, the different functional types are segregated into zones on the surface of the antenna (Figure 1C); segregation is also observed for the different functional types of s. coeloconica (Figure 1D). This zonal organization is less conspicuous for the large and small s. basiconica, of which different functional types are intermingled (Figures 1E-F). Electrophysiological data suggest that there are on the order of thirty different classes of olfactory receptors in the antenna, a rough estimate based upon the odor response profiles of individual olfactory receptors (and in a few cases, the assumption that the neurons of particular functional types of sensilla have unique response profiles).

In contrast to the antenna, the organization of the approximately 120 olfactory

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receptors of the maxillary palp is less complex. There are approximately 60 s. basiconica on the maxillary palp, each housing two olfactory receptors (Singh & Nayak, (1985) Int. J. Insect Morphol. Embryol. 14, 291-306). The 120 olfactory receptors fall into six different classes based upon their odorant response profiles (Clyne et al., (1999) Neuron 22, 339-347; de Bruyne et al., (1999) J. Neurosci. 19, 4520-4532). Neurons of the six ORN classes are always found in characteristic pairs in three functional types of s. basiconica, with the total number of neurons in each class being equal. Each class is distributed broadly over all, or almost all, of the olfactory surface of the maxillary palp.

Thus electrophysiological and anatomical studies suggest that there are on the order of thirty-five classes of olfactory receptors in the adult fly (approximately thirty on the antenna and six on the palp), each class with a distinct odor sensitivity. Classes of olfactory receptors found in the antenna are arrayed in zones, while the classes of olfactory receptors found in the maxillary palp are distributed in a less ordered fashion. olfactory receptors in both the maxillary palp and the antenna extend their axons to the antennal lobe of the brain, where first-order processing of olfactory information occurs. The lobe contains approximately forty olfactory glomeruli, spheroidal modules where ORN axons converge and where their terminal branches form synapses with the dendrites of their target interneurons (Stocker, (1994) Cell Tissue Res. 275, 3-26; Hildebrand & Shepherd, (1997) Annu. Rev. Neurosci. 20, 595-631).

One possibility underlying the molecular basis for distinct odor sensitivities for different classes of olfactory receptors is that each class of ORN expresses a unique odorant receptor, as has been proposed for vertebrate olfactory systems (Ngai et al., (1993) Cell 72, 667-680; Ressler et al., (1993) Cell 73, 597-609; Vassar et al., (1993) Cell 74, 309-318; Buck, (1996) Annu. Rev. Neurosci. 19, 517-544; Hildebrand & Shepherd, (1997) Annu. Rev. Neurosci. 20, 595-631). Alternatively, each class of ORN might express a unique combination of a large set of receptors, as found in chemosensory cells of the nematode, *C. elegans* (Troemel et al., (1995) Cell 83, 207-218). Both models call for a family of receptor genes, and several lines of evidence suggest that for insects such a

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family would belong to the superfamily of seven-transmembrane G protein-coupled receptors (GPCRs). First, there is evidence that insects generate responses to odorants via GPCR-activated second-messenger systems. For example, a rapid and transient increase in inositol 1,4,5-trisphosphate (IP3) has been observed in response to stimulation with pheromone and other odors using antennal preparations from various insect species (Breer et al., (1990) Nature 345, 65-68; Boekhoff et al., (1993) Insect Bjochem, Mol. Bjol. 23. 757-762; Wegener et al., (1993) J. Insect Physiol. 39, 153-163). This increase in IP3 can be blocked by pertussis toxin, implicating a G protein signaling cascade (Boekhoff et al., (1990) Cell. Signal. 2, 49-56). In Drosophila, norpA mutants, which lack the phospholipase C that is an essential component of phototransduction, also exhibit reduced olfactory responses of the maxillary palp (Riesgo-Escovar et al., (1995) J. Comp. Physiol. A180, 151-160). A second reason to suspect that odorant receptors in Drosophila are GPCRs is that GPCRs have been shown to be odorant receptors in both vertebrates and C. elegans; moreover, abundant evidence indicates that olfactory information in these other organisms is transduced by GPCR-activated second messenger systems (Buck. (1996) Annu. Rev. Neurosci. 19, 517-544; Bargmann & Kaplan, (1998) Annu. Rev. Neurosci. 21, 279-308). It would thus seem unlikely that a family of receptors that have a completely novel structure and that use a completely different transduction mechanism would have arisen in insects.

There have been extensive efforts to identify odorant and pheromone receptors in a variety of insects using a wide range of strategies. These efforts have been driven in part by interest in analyzing receptor genes in the context of highly tractable experimental systems in which there is a wealth of knowledge about olfactory function and organization. For example, *Drosophila* offers the advantages of a model genetic organism together with the ability to measure olfactory function conveniently *in vivo*, through either physiological or behavioral means. Interest in insect odorant receptors has also arisen because of the critical role of olfaction in the attraction of many insect pests to their plant hosts, of insect vectors of disease to their human hosts, and of insects to their

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mates. Nevertheless, efforts to identify odorant receptors in insects, based upon searches for genes bearing sequence similarities to odorant receptor genes from other organisms, or on other strategies, have been unsuccessful.

Applicants have discovered a novel multigene family encoding candidate odorant receptors that were identified from the *Drosophila* genomic sequence database. The forty-nine genes described here were discovered using novel computer programs that identify diagnostic features of the protein structure of the seven-transmembrane GPCR superfamily. Members of this new family are highly divergent from previously defined genes. Nearly all of the genes are found to be expressed in one or both of the olfactory organs, and for a number of genes expression is restricted to a subset of olfactory receptors. Applicant's further demonstrate that expression of different genes is initiated at different times during the development of the adult antenna, and that expression of a subset of these candidate receptor genes depends on the POU domain transcription factor, Acj6 (abnormal chemosensory jump 6).

SUMMARY OF THE INVENTION

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This invention provides isolated nucleic acid molecules including the following:

- a) isolated nucleic acid molecules that encode the amino acid sequences of *Drosophila* Odorant Receptor proteins;
- b) isolated nucleic acid molecules that encode protein fragments of at least 6 amino acids of a *Drosophila* Odorant Receptor proteins; and
- c) isolated nucleic acid molecules which hybridize to nucleic acid molecules which include nucleotide sequences encoding *Drosophila* Odorant Receptor proteins under conditions of sufficient stringency to produce a clear signal.
- This invention also provides such isolated nucleic acid molecules wherein the nucleic acids include at least one exon-intron boundary located in one of the following positions:
 - a) the nucleotides encoding the amino acids which include the third extracellular

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domain of a Drosophila Odorant Receptor protein;

- b) the nucleotides encoding the amino acids which include the fourth extracellular domain of a Drosophila Odorant Receptor protein; and
- c) the nucleotides encoding the amino acids which include the fourth intracellular domain of a *Drosophila* Odorant Receptor protein.

This invention further provides such isolated nucleic acid molecules which have the nucleic acid sequence of one of the following sequences: SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95 and 97.

This invention also provides such isolated nucleic acid molecules operably linked to one or more expression control elements.

This invention further provides vectors which include any of the aforementioned nucleic acid molecules and host cells which include such vectors..

This invention also provides host cells transformed so as to contain any of the aforementioned nucleic acid molecules, wherein such host cells can be either prokaryotic host cells or eukaryotic host cells.

This invention also provides methods for producing proteins or protein fragments wherein the methods include transforming host cells with any of the aforementioned nucleic acids under conditions in which the protein or protein fragment encoded by said nucleic acid molecule is expressed. This invention also provides such methods wherein the host cells are either prokaryotic host cells or eukaryotic host cells. This invention further provides isolated proteins or protein fragments produced by such methods.

This invention provides isolated proteins or protein fragments which include:

- a) isolated proteins encoded by one of the following amino acid sequences: SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96 and 98:
 - b) isolated protein fragments which include at least 6 amino acids of any of the

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following sequences: SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96 and 98;

- c) isolated proteins which include conservative amino acid substitutions of any of the following sequences: SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96 and 98; and
- d) naturally occurring amino acid sequence variants of any of the following sequences: SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96 and 98.

The present invention further provides such isolated proteins or protein fragments which include at least one of the following conserved amino acids:

- a) Leucine in the third extracellular domain of a Drosophila Odorant Receptor protein;
- b) Histidine in the third extracellular domain of a *Drosophila* Odorant Receptor protein;
- c) Cysteine in the sixth transmembrane domain of a Drosophila Odorant Receptor protein;
- d) Tryptophan in the fourth extracellular domain of a *Drosophila* Odorant Receptor protein;
- e) Glutamine in the seventh transmembrane domain of a *Drosophila* Odorant Receptor protein;
- f) Proline in the seventh transmembrane domain of a Drosophila Odorant Receptor protein;
- g) Alanine in the fourth intracellular domain of a Drosophila Odorant Receptor protein; and
 - h) Tyrosine in the fourth intracellular domain of a Drosophila Odorant Receptor

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protein.

The present invention also provides isolated antibodies that bind to any of the aforementioned polypeptides.

The present invention also provides such antibodies which are either monoclonal antibodies or polyclonal antibodies.

This invention also provides methods of identifying agents which modulate the expression of any of the aforementioned proteins or protein fragments by:

- a) exposing cells which express the proteins or protein fragments to the agents;
 and
- b) determining whether the agent modulates expression of said proteins or protein fragments, thereby identifying agents which modulate the expression of the proteins or protein fragments.

The present invention also provides methods of identifying agents which modulate the activity of any of the aforementioned proteins or protein fragments by:

- a) exposing cells which express the proteins or protein fragments to the agents;
 and
- b) determining whether the agents modulate the activity of said proteins or protein fragments, thereby identifying agents which modulate the activity of the proteins or protein fragments.

The present invention also provides such methods where the agent modulates at least one activity of the proteins or protein fragments.

This invention provides methods of identifying agents which modulate the transcription of any of the aforementioned nucleic acid molecules by:

- a) exposing cells which transcribe the nucleic acids to the agents; and
- b) determining whether the agents modulate transcription of said nucleic acids, thereby identifying agents which modulate the transcription of the nucleic acid.

This invention further provides methods of identifying binding partners for the aforementioned proteins or protein fragments by:

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- a) exposing said proteins or protein fragments to potential binding partners; and
- b) determining if the potential binding partners bind to said proteins or protein fragments, thereby identifying binding partners for the proteins or protein fragments.

The present invention also provides methods of modulating the expression of nucleic acids encoding the aforementioned proteins or protein fragments by administering an effective amount of agents which modulate the expression of the nucleic acids encoding the proteins or protein fragments.

This invention also provides methods of modulating at least one activity of the aforementioned proteins or protein fragments by administering an effective amount of the agents which modulate at least one activity of the proteins or protein fragments.

This invention provides methods of identifying novel olfactory receptor genes by:

- a) selecting candidate olfactory receptor genes by screening nucleic acid databases using an algorithm trained to identify seven transmembrane receptors genes;
- b) screening said selected candidate olfactory receptor genes by identifying nucleic acid sequences with conserved amino acid residues and intron-exon boundaries common to olfactory receptors, and having open reading frames of sufficient size so as to encode a seven transmembrane receptor; and
- c) identifying the novel olfactory receptor genes and measuring the expression of olfactory receptor genes wherein the detection of expression confirms said candidate olfactory genes as olfactory genes.

This invention also provides methods of identifying novel olfactory receptor genes by:

- a) selecting candidate olfactory receptor genes by screening nucleic acid databases for nucleic acid sequences with sufficient homology to at least one known olfactory receptor gene;
- b) screening said selected candidate olfactory receptor genes by identifying nucleic acids with conserved amino acid residues and intron-exon boundaries common to olfactory receptors, and having open reading frames of sufficient size so as to encode a

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seven transmembrane receptor; and

c) identifying the novel olfactory receptor genes and measuring the expression of olfactory receptor genes wherein the detection of expression confirms said candidate olfactory genes as olfactory genes.

The present invention also provides transgenic insects modified to contain any of the aforementioned nucleic acid molecules.

This invention also provides such transgenic insects, wherein the nucleic acid molecules contain mutations that alter expression of the encoded proteins.

10 BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 An overview of the olfactory system of the adult Drosophila. (A) The two olfactory organs of the adult fly, the third antennal segment (arrow) and the maxillary palp (arrowhead), scale bar = 100 μ m. (B) Higher magnification of part of a third antennal segment showing the morphological categories of olfactory sensilla: s. basiconica [B], s. trichodea [T] and s. coeloconica [C], scale bar = 5 μ m. (C-F) Diagram of the olfactory sensilla on the anterior face of the third antennal segment. The different morphological categories of sensilla are indicated by different shapes, and the colors indicate different functional types of sensilla within each morphological category. Dorsal is at the top and medial is to the left. (C) Distribution of different functional types of s. trichodea. (D) Distribution of different functional types of s. coeloconica. (E) The large s. basiconica are densely clustered in a small dorso-medial region, where the different functional types are intermingled. For simplicity, only two types are shown. (F) The small s. basiconica are widely dispersed, and the different functional types are intermingled.

Figure 2 Genomic organization and hydropathy plots of DOR genes. (A) Genomic organization of DOR genes (not to scale). The genes shown are those identified from 16% of the total genomic sequence; most of the available sequence is from Chromosome

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2. The approximate chromosomal location of each gene is indicated. Genes separated by less than one kilobase are jointly underlined. Within each cluster, all genes are oriented in the same direction. The transcriptional orientation of the DOR genes with respect to the chromosome is unknown for 2F.1, 25A.1, 47E.2, 59D.1, and the cluster at 33B. (B) The 2F.1 gene is flanked by two closely linked genes, fs(1)k10 and crn. The arrowheads indicate the 3' end of each gene; for 2F.1 the end of the arrow indicates the position of the polyA+ addition signal sequence. (C) Hydropathy plots of the genes whose expression patterns are shown in Figures 4-6. Hydrophobic peaks predicted by Kyte-Doolittle analysis appear above the center line. The approximate positions of the seven putative transmembrane domains are indicated above the first hydropathy plot.

Figure 3 Amino acid sequence alignment of DOR genes. All DNA sequences were obtained from the BDGP database, and the determination of predicted amino acid sequences is described in the Examples. Residues conserved in >50% of the predicted proteins are shaded. The approximate locations of predicted transmembrane domains 1-7 are indicated. Exon-intron boundaries are shown with vertical lines.

Figure 4 DOR genes are expressed in subsets of olfactory receptor neurons in the maxillary palp. In situ hybridizations to tissue sections of maxillary palps. Panel A shows a frontal section; all other sections are sagittal. (A) A 46F.1 probe reveals expression in a subset of olfactory receptors which are broadly distributed. The background staining at the periphery of the organ represents non-specific labeling of the cuticle, observed equally for sense and antisense probes. (B) A 33B.3 probe also hybridizes to a subset of cells. Unlabeled olfactory receptors are visible under the cuticular surface (top center). (C) At higher magnification it can be seen that the cells expressing 46F.1 are neurons. Note the axons projecting from the cells into the nerve (n) which runs through the middle of the maxillary palp. The arrowhead indicates an ORN which is not expressing 46F.1, adjacent to an ORN which is strongly stained. The light

staining of the nerve is background staining, observed equally for sense and antisense probes. (D) 33B.3 is not expressed in the acj6 null mutant, acj6⁶.

Figure 5 DOR genes are expressed in subsets of antennal cells. Shown are *in situ* hybridizations to tissue sections of third antennal segments. In panels A, B, D, and F the plane of section passes through the fluid-filled interior of the antenna. (A,B) A 47E.1 probe hybridizes to a subset of cells which are broadly distributed. (C,D) A 25A.1 probe hybridizes to a smaller subset of cells. The angle of section in panel C differs somewhat from the other panels. (E) A 22A.2 probe hybridizes to a subset of cells in the dorso-medial region where the large s. basiconica are located. (F) 22A.2 is expressed in the $acj6^6$ mutant, in contrast to 33B.3 (Figure 4D). (G) Summary of distributions of labeled cells for 47E.1 (open circles), 25A.1 (black dots), and 22A.2 (gray dots) on the anterior face of the antenna, based on analysis of expression in 30-50 antennae for each gene.

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Figure 6 Expression of DOR genes during antennal development. In situ hybridizations to tissue sections of third antennal segments at different times during pupal development. The times indicated refer to hours APF (after puparium formation). Arrows indicate labeled cells. (A) Expression of 22A.2 is not observed at 54 hours APF. Note that background staining is absent in sections taken at 54 hours (or at earlier times), presumably due to the immaturity of the cuticle. (B) Expression of 22A.2 is observed at 60 hours APF. (C) 47E.1 expression is not observed at 72 hours APF. Background staining is observed with both sense and antisense probes on the cuticular surface of the sacculus (s), a multi-chambered sensory pit and the dot at the bottom of the third antennal segment is non-specific staining of a section of tracheal tissue. (D) Expression of 47E.1 is detected at 93 hours APF. (E) The odor binding protein OS-E is not expressed at 72 hours APF. The small dots at the bottom of the antenna are non-specific staining of a section of tracheal tissue, observed with both sense and antisense probes. (F) Abundant

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expression of OS-E is seen at 93 hours APF.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

I. Specific Embodiments

A. Drosophila Olfactory Receptor Proteins

The present invention provides a family of isolated proteins, allelic variants of the proteins, and conservative amino acid substitutions of the proteins. As used herein, protein or polypeptide refers to any one of the proteins that has the amino acid sequence depicted in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96 and 98. The invention also includes naturally occurring allelic variants and proteins that have a slightly different amino acid sequence than that specifically recited above. Allelic variants, though possessing a slightly different amino acid sequence than those recited above, will still have the same or similar biological functions associated with any of the amino acid proteins.

As used herein, the family of proteins related to any one of the amino acid sequences depicted in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96 and 98 refers to proteins that have been isolated from organisms in addition to *Drosophila*. The methods used to identify and isolate other members of the family of proteins related to these amino acid proteins are described below.

The proteins of the present invention are preferably in isolated form. As used herein, a protein is said to be isolated when physical, mechanical or chemical methods are employed to remove the protein from cellular constituents that are normally associated with the protein. A skilled artisan can readily employ standard purification methods to obtain an isolated protein.

The proteins of the present invention further include conservative amino acid substitution variants (i.e., conservative) of the proteins herein described. As used herein,

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a conservative variant refers to at least one alteration in the amino acid sequence that does not adversely affect the biological functions of the protein. A substitution, insertion or deletion is said to adversely affect the protein when the altered sequence prevents or disrupts a biological function associated with the protein. For example, the overall charge, structure or hydrophobic-hydrophilic properties of the protein can be altered without adversely affecting a biological activity. Accordingly, the amino acid sequence can often be altered, for example to render the peptide more hydrophobic or hydrophilic, without adversely affecting the biological activities of the protein.

Ordinarily, the allelic variants, the conservative substitution variants, and the members of the protein family, will have an amino acid sequence having at least 30% amino acid sequence identity with the sequences set forth in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96 and 98 more preferably at least 35%, even more preferably at least 40%, and most preferably at least 45%. Identity or homology with respect to such sequences is defined herein as the percentage of amino acid residues in the candidate sequence that are identical with the known peptides, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent homology, and not considering any conservative substitutions as part of the sequence identity. N-terminal, C-terminal or internal extensions, deletions, or insertions into the peptide sequence shall not be construed as affecting homology.

In addition to amino acid sequence identity, the proteins of the present invention have seven transmembrane domains as defined by hydropathy analysis (Kyte & Doolittle, (1982) J. Mol. Biol. 157, 105-132). Furthermore, the proteins of the present invention have conserved amino acid residues in defined domains of the protein. For example, the proteins of the present invention have at least one of the following conserved amino acids as depicted in Figure 3, including but not limited to, Leucine in the third extracellular domain; Histidine in the third extracellular domain; Histidine in the third extracellular domain; Cysteine in the sixth transmembrane

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domain; Tryptophan in the fourth extracellular domain; Glutamine in the seventh transmembrane domain; Proline in the seventh transmembrane domain; Alanine in the fourth intracellular domain; or Tyrosine in the fourth intracellular domain. In addition, the conserved amino acids may be selected from any of the amino acid residues indicated as being conserved among DOR proteins as depicted in Figure 3 (shaded).

Thus, the proteins of the present invention include molecules having the amino acid sequence disclosed in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96 and 98; fragments thereof having a consecutive sequence of at least about 3, 4, 5, 6, 10, 15, 20, 25, 30, 35 or more amino acid residues of the proteins, for instance, antigenic fragments such as those found in the extracellular domains of the protein (see Figure 3); amino acid sequence variants wherein an amino acid residue has been inserted N- or C-terminal to, or within, the disclosed sequence; and amino acid sequence variants of the disclosed sequences, or their fragments as defined above, that have been substituted by another residue. Contemplated variants further include those containing predetermined mutations by, e.g., homologous recombination, site-directed or PCR mutagenesis, and the corresponding proteins of other insect species, including but not limited to the order Diptera, Lepidoptera, Homopterera and Coleoptera, within these orders, preferably the genus Drosophila, Anopheles, Aedes, Ceratitis, Muscidae, Culicidae, Anagasta and Popilla and the alleles or other naturally occurring variants of the family of proteins; and derivatives wherein the protein has been covalently modified by substitution, chemical, enzymatic, or other appropriate means with a moiety other than a naturally occurring amino acid (for example a detectable moiety such as an enzyme or radioisotope).

As described below, members of the family of proteins can be used: 1) to identify agents which modulate at least one activity of the protein; 2) to identify binding partners for the protein, 3) as an antigen to raise polyclonal or monoclonal antibodies, and 4) in methods to modify insect behavior.

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B. Nucleic Acid Molecules

The present invention further provides nucleic acid molecules which encode any of the proteins having SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78. 80, 82, 84, 86, 88, 90, 92, 94, 96 and 98 and the related proteins herein described, preferably in isolated form. As used herein, "nucleic acid" is defined as RNA or DNA that encodes a protein or peptide as defined above, is complementary to a nucleic acid sequence encoding such peptides, hybridizes to such a nucleic acid and remains stably bound to it under appropriate stringency conditions, or encodes a polypeptide sharing at least 75% sequence identity, preferably at least 80%, and more preferably at least 85%, with the peptide sequences in conserved domains. Specifically contemplated are genomic DNA, cDNA, mRNA and antisense molecules, as well as nucleic acids based on alternative backbones or including alternative bases whether derived from natural sources or synthesized. Such hybridizing or complementary nucleic acids, however, are defined further as being novel and non-obvious over any prior art nucleic acid including that which encodes, hybridizes under appropriate stringency conditions, or is complementary to nucleic acid encoding a protein according to the present invention.

Homology or identity at the amino acid or nucleotide level is determined by BLAST (Basic Local Alignment Search Tool) analysis using the algorithm employed by the programs blastp, blastn, blastx, tblastn and tblastx (Karlin et al., (1990) Proc. Natl. Acad. Sci. USA 87, 2264-2268 and Altschul, (1993) J. Mol. Evol. 36, 290-300, fully incorporated by reference) which are tailored for sequence similarity searching. The approach used by the BLAST program is to first consider similar segments between a query sequence and a database sequence, then to evaluate the statistical significance of all matches that are identified and finally to summarize only those matches which satisfy a preselected threshold of significance. For a discussion of basic issues in similarity searching of sequence databases (see Altschul et al., (1994) Nature Genetics 6, 119-129

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which is fully incorporated by reference). The search parameters for histogram, descriptions, alignments, expect (i.e., the statistical significance threshold for reporting matches against database sequences), cutoff, matrix and filter are at the default settings. The default scoring matrix used by blastp, blastx, tblastn, and tblastx is the BLOSUM62 matrix (Henikoff et al., (1992) Proc. Natl. Acad. Sci. USA 89, 10915-10919, fully incorporated by reference). For blastn, the scoring matrix is set by

10915-10919, fully incorporated by reference). For **blastn**, the scoring matrix is set by the ratios of M (*i.e.*, the reward score for a pair of matching residues) to N (*i.e.*, the penalty score for mismatching residues), wherein the default values for M and N are 5 and -4, respectively.

"Stringent conditions" are those that (1) employ low ionic strength and high temperature for washing, for example, 0.5 M sodium phosphate buffer at pH 7.2, 1 mM EDTA at pH 8.0 in 7% SDS at either 65°C or 55°C, or (2) employ during hybridization a denaturing agent such as formamide, for example, 50% formamide with 0.1% bovine serum albumin, 0.1% Ficoll, 0.1% polyvinylpyrrolidone, 0.05 M sodium phosphate buffer at pH 6.5 with 0.75 M NaCl, 0.075 M sodium citrate at 42°C. Another example is use of 50% formamide, 5× SSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate at pH 6.8, 0.1% sodium pyrophosphate, 5× Denhardt's solution, sonicated salmon sperm DNA (50 μ g/ml), 0.1% SDS and 10% dextran sulfate at 55°C, with washes at 55°C in 0.2× SSC and 0.1% SDS. A skilled artisan can readily determine and vary the stringency conditions appropriately to obtain a clear and detectable hybridization signal. Preferred molecules are those that hybridize under the above conditions to the complements of SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95 and 97, and which encode a functional protein.

As used herein, a nucleic acid molecule is said to be "isolated" when the nucleic acid molecule is substantially separated from contaminant nucleic acid encoding other polypeptides from the source of nucleic acid.

The present invention further provides fragments of any one of the encoding nucleic

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acids molecules. As used herein, a fragment of an encoding nucleic acid molecule refers to a small portion of the entire protein coding sequence. The size of the fragment will be determined by the intended use. For example, if the fragment is chosen so as to encode an active portion of the protein, the fragment will need to be large enough to encode the functional region(s) of the protein. For instance, fragments of the invention encode antigenic fragments such as the extracellular loops or N-terminal domain of the protein depicted in SEQ ID NO: 2 and as set forth in Figure 3. If the fragment is to be used as a nucleic acid probe or PCR primer, then the fragment length is chosen so as to obtain a relatively small number of false positives during probing and priming.

Fragments of the encoding nucleic acid molecules of the present invention (*i.e.*, synthetic oligonucleotides) that are used as probes or specific primers for the polymerase chain reaction (PCR), or to synthesize gene sequences encoding proteins of the invention can easily be synthesized by chemical techniques, for example, the phosphotriester method of Matteucci *et al.*, (1981) J. Am. Chem. Soc. 103, 3185-3191) or using automated synthesis methods. In addition, larger DNA segments can readily be prepared by well known methods, such as synthesis of a group of oligonucleotides that define various modular segments of the gene, followed by ligation of oligonucleotides to build the complete modified gene.

The encoding nucleic acid molecules of the present invention may further be modified so as to contain a detectable label for diagnostic and probe purposes. A variety of such labels are known in the art and can readily be employed with the encoding molecules herein described. Suitable labels include, but are not limited to, fluorescent-labeled, biotin-labeled, radio-labeled nucleotides and the like. A skilled artisan can employ any of the art known labels to obtain a labeled encoding nucleic acid molecule.

Modifications to the primary structure itself by deletion, addition, or alteration of the amino acids incorporated into the protein sequence during translation can be made without destroying the activity of the protein. Such substitutions or other alterations result in proteins having an amino acid sequence encoded by a nucleic acid falling within the contemplated scope of the present invention.

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C. Isolation of Other Related Nucleic Acid Molecules

As described above, the identification and characterization of the nucleic acid molecules having SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95 and 97 allows a skilled artisan to isolate nucleic acid molecules that encode other members of the protein family in addition to the sequences herein described. Further, the presently disclosed nucleic acid molecules allow a skilled artisan to isolate nucleic acid molecules that encode other members of the family of proteins in addition to the protein having SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96 and 98.

Essentially, a skilled artisan can readily use any one of the amino acid sequences selected from SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96 and 98, to generate antibody probes to screen expression libraries prepared from appropriate cells. Typically, polyclonal antiserum from mammals such as rabbits immunized with the purified protein (as described below) or monoclonal antibodies can be used to probe a cDNA or genomic expression library to obtain the appropriate coding sequence for other members of the protein family. The cloned cDNA sequence can be expressed as a fusion protein, expressed directly using its own control sequences, or expressed by constructions using control sequences appropriate to the particular host used for expression of the enzyme.

Alternatively, a portion of the coding sequence herein described can be synthesized and used as a probe to retrieve DNA encoding a member of the protein family from any organism. Oligomers containing approximately 18-20 nucleotides (encoding about a six to seven amino acid stretch) are prepared and used to screen genomic DNA or cDNA libraries to obtain hybridization under stringent conditions or conditions of sufficient stringency to

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eliminate an undue level of false positives.

Additionally, pairs of oligonucleotide primers can be prepared for use in a polymerase chain reaction (PCR) to selectively clone an encoding nucleic acid molecule. A PCR denature/anneal/extend cycle for using such PCR primers is well known in the art and can readily be adapted for use in isolating other encoding nucleic acid molecules. For example, degenerate primers can be used to clone any DOR gene across species. Specifically, based on the sequence information derived from the family of DORs, degenerate primers can be designed based on conserved sequences among olfactory receptors, which can then be used to clone nucleic acid molecules encoding olfactory receptor proteins from other species of insects.

Applicants have also identified a method for isolating nucleic acid molecules that encode other members of the protein family in addition to the sequences herein described. Essentially, a two-step strategy is employed to identify odorant receptor genes from the genomic database. First, a computer algorithm was designed to search genomic sequences for open reading frames (ORFs) from candidate odorant receptor genes. Second, RT-PCR is used to determine if transcripts from any of these ORFs are expressed in olfactory organs.

The algorithm is used to identify GPCR genes using statistical characterization of amino acid physico-chemical profiles in combination with a non-parametric discriminant function. The algorithm is trained on a set of putative sequences from a database. In the first step, three sets of descriptors are used to summarize the physico-chemical profiles of the sequences. These are GES scale of hydropathy (Engelman et al., (1986) Annu. Rev. Biophys. Biophys. Chem. 15, 321-353), polarity (Brown, (1991) Molecular Biology Labfax, Academic Press), and amino acid usage frequency. For the first two of these measurements, a computed sliding window profile is employed (White, (1994) Membrane Protein Structure, Oxford University Press) using a kernel of a certain number of amino acids as a constant function convoluted with a certain number of amino acids as a Gaussian function. These profiles are then summarized with three statistics; the periodicity, average derivative and the variance of the derivative.

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Each sequence is then characterized by multiple variables using a non-parametric linear discriminant function that is optimized to separate the known family proteins from random proteins in the training set. The same linear discriminant function with the scores derived from the training set is used to screen any nucleic acid database for candidate genes. The candidate sequences are given significance values by an odds ratio of the proteins and non-family proteins, computed using the observed empirical distribution of the training set. Those sequences with a sufficiently high odds ratio are considered for further analysis. The algorithm can also be used to identify any protein family by altering the training set of sequences.

The method of identification further includes steps for identifying novel olfactory receptor genes comprising selecting candidate olfactory receptor genes by screening a nucleic acid database using an algorithm trained to identify seven transmembrane receptors genes; screening said selected candidate olfactory receptor genes by identifying nucleic acid sequences with conserved amino acid residues and intron-exon boundaries common to olfactory receptors, and open reading frames of sufficient size as to encode a seven transmembrane receptor. As an additional step, the expression of olfactory receptor genes is measured to confirm candidate olfactory gene as an olfactory gene. The exon-intron boundaries and conserved amino acid residues may be selected from any of the positions depicted in Figure 3. Alternatively, selecting candidate olfactory receptor genes by screening a nucleic acid database for nucleic acid sequences with sufficient homology to at least one known olfactory receptor gene is also encompassed in the invention. In a preferred embodiment, the nucleic acid database is a genomic database, an EST database or even an olfactory receptor database as previously described (Skoufos *et al.*, (1999) Nucleic Acids Research 27, 343-345).

In one example of the invention, the training set could consist of a subset of seven transmembrane proteins such as dopaminergic receptors and could be used to search genomic sequences for new subtypes of dopaminergic receptors. In another example, the training set could consist of ion channels and could be used to identify new subtypes of ion channels in a

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particular family. In yet another example, the training set could consist of known sequences coding for a receptors from a particular family and could be used to identify homologs across species. Specifically, olfactory receptors of one species could be used as a training set to identify olfactory receptors in another species.

D. rDNA molecules containing a DNA molecule

The present invention further provides recombinant DNA molecules (rDNAs) that contain a coding sequence. As used herein, a rDNA molecule is a DNA molecule that has been subjected to molecular manipulation *in situ*. Methods for generating rDNA molecules are well known in the art, for example, see Sambrook *et al.*, (1985) Molecular Cloning - A Laboratory Manual, Cold Spring Harbor Laboratory Press. In the preferred rDNA molecules, a coding DNA sequence is operably linked to expression control sequences or vector sequences.

The choice of vector and expression control sequences to which one of the protein family encoding sequences of the present invention is operably linked depends directly, as is well known in the art, on the functional properties desired, e.g., protein expression, and the host cell to be transformed. A vector contemplated by the present invention is at least capable of directing the replication or insertion into the host chromosome, and preferably also expression, of the structural gene included in the rDNA molecule.

Expression control elements that are used for regulating the expression of an operably linked protein encoding sequence are known in the art and include, but are not limited to, inducible promoters, constitutive promoters, secretion signals, and other regulatory elements. Preferably, the inducible promoter is readily controlled, such as being responsive to a nutrient in the host cell's medium.

In one embodiment, the vector containing a coding nucleic acid molecule will include a prokaryotic replicon, i.e., a DNA sequence having the ability to direct autonomous replication and maintenance of the recombinant DNA molecule extra-chromosomally in a prokaryotic host cell, such as a bacterial host cell, transformed therewith. Such replicons are

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well known in the art. In addition, vectors that include a prokaryotic replicon may also include a gene whose expression confers a detectable marker such as a drug resistance. Typical bacterial drug resistance genes are those that confer resistance to ampicillin or tetracycline.

Vectors that include a prokaryotic replicon can further include a prokaryotic or bacteriophage promoter capable of directing the expression (transcription and translation) of the coding gene sequences in a bacterial host cell, such as *E. coli*. A promoter is an expression control element formed by a DNA sequence that permits binding of RNA polymerase and transcription to occur. Promoter sequences compatible with bacterial hosts are typically provided in plasmid vectors containing convenient restriction sites for insertion of a DNA segment of the present invention. Typical of such vector plasmids are pUC8, pUC9, pBR322 and pBR329 available from BioRad Laboratories, pPL and pKK223 available from Pharmacia.

Expression vectors compatible with eukaryotic cells, preferably those compatible with vertebrate cells such as insect cells, can also be used to form a rDNA molecules that contains a coding sequence. Eukaryotic cell expression vectors are well known in the art and are available from several commercial sources. Typically, such vectors are provided containing convenient restriction sites for insertion of the desired DNA segment. Typical of such vectors are pSVL and pKSV-10 (Pharmacia), pBPV-1/pML2d (International Biotechnologies, Inc.), pTDT1 (ATCC, #31255), the vector pCDM8 described herein, and the like eukaryotic expression vectors. Vectors may be modified to include insect cell specific promoters if needed.

Eukaryotic cell expression vectors used to construct the rDNA molecules of the present invention may further include a selectable marker that is effective in an eukaryotic cell, preferably a drug resistance selection marker. A preferred drug resistance marker is the gene whose expression results in neomycin resistance, i.e., the neomycin phosphotransferase (neo) gene (Southern et al., (1982) J. Mol. Appl. Genet. 1, 327-341). Alternatively, the selectable marker can be present on a separate plasmid, and the two vectors are introduced by

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co-transfection of the host cell, and selected by culturing in the appropriate drug for the selectable marker.

E. Host Cells Containing an Exogenously Supplied Coding Nucleic Acid

The present invention further provides host cells transformed with a nucleic acid molecule that encodes a protein of the present invention. The host cell can be either prokaryotic or eukaryotic. Eukaryotic cells useful for expression of a protein of the invention are not limited, so long as the cell line is compatible with cell culture methods and compatible with the propagation of the expression vector and expression of the gene product. Preferred eukaryotic host cells include, but are not limited to, yeast, insect and mammalian cells, preferably insect cells such as those from a *Drosophila* cell line. Preferred *Drosophila* host cells include *Drosophila* Schneider line 2, and the like insect tissue culture cell lines.

Any prokaryotic host can be used to express a rDNA molecule encoding a protein of the invention. The preferred prokaryotic host is *E. coli*.

Transformation of appropriate cell hosts with a rDNA molecule of the present invention is accomplished by well known methods that typically depend on the type of vector used and host system employed. With regard to transformation of prokaryotic host cells, electroporation and salt treatment methods are typically employed, see, for example, Cohen et al., (1972) Proc. Natl. Acad. Sci. USA 69, 2110-2114; and Maniatis et al., (1982) Molecular Cloning - A Laboratory Manual, Cold Spring Harbor Laboratory Press. With regard to transformation of vertebrate cells with vectors containing rDNAs, electroporation, cationic lipid or salt treatment methods are typically employed, see, for example, Graham et al., (1973) Virology 52, 456-467; and Wigler et al., (1979) Proc. Natl. Acad. Sci. USA 76, 1373-1376.

Successfully transformed cells, i.e., cells that contain a rDNA molecule of the present invention, can be identified by well known techniques including the selection for a selectable marker. For example, cells resulting from the introduction of an rDNA of the present invention can be cloned to produce single colonies. Cells from those colonies can be harvested, lysed and their DNA content examined for the presence of the rDNA using a

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method such as that described by Southern, (1975) J. Mol. Biol. 98, 503-517; or Berent *et al.*, (1985) Biotech. Histochem. 3, 208; or the proteins produced from the cell assayed via an immunological method.

5 F. Production of Recombinant Proteins using a rDNA Molecule

The present invention further provides methods for producing a protein of the invention using nucleic acid molecules herein described. In general terms, the production of a recombinant form of a protein typically involves the following steps: First, a nucleic acid molecule is obtained that encodes a protein of the invention, such as any of the nucleic acid molecule depicted in SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95 and 97. The nucleic acid molecule is then preferably placed in operable linkage with suitable control sequences, as described above, to form an expression unit containing the protein open reading frame. The expression unit is used to transform a suitable host and the transformed host is cultured under conditions that allow the production of the recombinant protein. Optionally the recombinant protein is isolated from the medium or from the cells; recovery and purification of the protein may not be necessary in some instances where some impurities may be tolerated.

Each of the foregoing steps can be done in a variety of ways. For example, the desired coding sequences may be obtained from genomic fragments and used directly in appropriate hosts. The construction of expression vectors that are operable in a variety of hosts is accomplished using appropriate replicons and control sequences, as set forth above. The control sequences, expression vectors, and transformation methods are dependent on the type of host cell used to express the gene and were discussed in detail earlier. Suitable restriction sites can, if not normally available, be added to the ends of the coding sequence so as to provide an excisable gene to insert into these vectors. A skilled artisan can readily adapt any host-expression system known in the art for use with the nucleic acid molecules of the invention to produce recombinant protein.

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G. Methods to Identify Binding Partners

Another embodiment of the present invention provides methods for use in isolating and identifying binding partners of any of the DOR proteins of the invention. In detail, a protein of the invention is mixed with a potential binding partner or an extract or fraction of a cell under conditions that allow the association of potential binding partners with the protein of the invention. After mixing, peptides, polypeptides, proteins or other molecules that have become associated with a protein of the invention are separated from the mixture. The binding partner that bound to the protein of the invention can then be removed and further analyzed. To identify and isolate a binding partner, the entire protein, for instance a protein comprising the entire amino acid sequence of any of the proteins depicted in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96 and 98 can be used. Alternatively, a fragment of any of the proteins can be used.

As used herein, a cellular extract refers to a preparation or fraction which is made from a lysed or disrupted cell. The preferred source of cellular extracts will be cells derived from *Drosophila*, for instance, antennae and maxillary palp cellular extract.

A variety of methods can be used to obtain an extract of a cell. Cells can be disrupted using either physical or chemical disruption methods. Examples of physical disruption methods include, but are not limited to, sonication and mechanical shearing. Examples of chemical lysis methods include, but are not limited to, detergent lysis and enzyme lysis. A skilled artisan can readily adapt methods for preparing cellular extracts in order to obtain extracts for use in the present methods.

Once an extract of a cell is prepared, the extract is mixed with any of the proteins of the invention under conditions in which association of the protein with the binding partner can occur. A variety of conditions can be used, the most preferred being conditions that closely resemble conditions found in the cytoplasm of a *Drosophila* cell. Features such as osmolarity, pH, temperature, and the concentration of cellular extract used, can be varied to optimize the

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association of the protein with the binding partner.

After mixing under appropriate conditions, the bound complex is separated from the mixture. A variety of techniques can be utilized to separate the mixture. For example, antibodies specific to a protein of the invention can be used to immunoprecipitate the binding partner complex. Alternatively, standard chemical separation techniques such as chromatography and density-sediment centrifugation can be used.

After removal of non-associated cellular constituents found in the extract, the binding partner can be dissociated from the complex using conventional methods. For example, dissociation can be accomplished by altering the salt concentration or pH of the mixture.

To aid in separating associated binding partner pairs from the mixed extract, the protein of the invention can be immobilized on a solid support. For example, the protein can be attached to a nitrocellulose matrix or acrylic beads. Attachment of the protein to a solid support aids in separating peptide-binding partner pairs from other constituents found in the extract. The identified binding partners can be either a single protein or a complex made up of two or more proteins. Alternatively, binding partners may be identified using a Far-Western assay according to the procedures of Takayama *et al.*, (1997) Methods Mol. Biol. 69, 171-184 or identified through the use of epitope tagged proteins or GST fusion proteins.

Alternatively, the nucleic acid molecules of the invention can be used in a yeast twohybrid system. The yeast two-hybrid system has been used to identify other protein partner pairs (Alifragis et al., (1997) Proc. Natl. Acad. Sci. USA 94, 13099-13104; Dong et al., (1999) Gene 237, 421-428) and can readily be adapted to employ the nucleic acid molecules herein described.

In another embodiment, binding partners may be identified in insects using single unit recordings as previously described (Kaissling, (1995) Single unit and electroantennogram recordings in insect olfactory organs, in: Spielman & Brand (ed.) Experimental Cell Biology of Taste and Olfaction, CRC Press). Using single unit recordings *in vivo*, response profiles are established for potential ligands, these profiles are then categorized into distinct functional classes indicative of distinct receptor-ligand interactions (see, e.g., U.S. Patent No. 5,993,778).

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Single unit recordings in transgenic insects which contain transgenes resulting in over- or under-expression of a gene are also useful for identifying and characterizing ligands which bind to multiple olfactory receptors as well as identifying characterizing new olfactory receptors.

The nucleic acids of the invention and their corresponding proteins can be used on an array or microarray for high-throughput screening for agents which interact with either the nucleic acids of the invention or their corresponding proteins. An "array" or "microarray" generally refers to a grid system which has each position or probe cell occupied by a defined nucleic acid fragments also known as oligonucleotides. The arrays themselves are sometimes referred to as "chips" or "biochips". High-density nucleic acid and protein microarrays often have thousands of probe cells in a variety of grid styles.

A typical molecular detection chip includes a substrate on which an array of recognition sites, binding sites or hybridization sites are arranged. Each site has a respective molecular receptor which binds or hybridizes with a molecule having a predetermined structure. The solid support substrates which can be used to form surface of the array or chip include organic and inorganic substrates, such as glass, polystyrenes, polyimides, silicon dioxide and silicon nitride. For direct attachment of probes to the electrodes, the electrode surface must be fabricated with materials capable of forming conjugates with the probes.

Once the array is fabricated, a sample solution is applied to the molecular detection chip and molecules in the sample bind or hybridize at one or more sites. The sites at which binding occurs are detected, and one or more molecular structures within the sample are subsequently deduced. Detection of labeled batches is a traditional detection strategy and includes radioisotope, fluorescent and biotin labels, but other options are available, including electronic signal transduction.

Polymer arrays of nucleic acid probes can be used to extract information from, for example, nucleic acid samples. These samples are exposed to the probes under conditions that permit binding. The arrays are then scanned to determine to which probes the sample molecules have interacted with the nucleic acids of the polymer array. One can obtain

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information by careful probe selection and using algorithms to compare patterns of interactions. For example, the method is useful in screening for novel olfactory receptors in multiple organisms. For example, *Drosophila* degenerate olfactory receptor oligonucleotide arrays can be used to examine a nucleic acid sample from another insect species in order to identify novel olfactory receptors in that species.

In typical applications, a complex solution containing one or more substances to be characterized contacts a polymer array comprising nucleic acids. For example, the array is comprised of nucleic acid probes. The probes of the array can be either DNA or RNA, which may be either single-stranded or double-stranded. In a preferred embodiment of the invention, the probes are arranged (either by immobilization, typically by covalent attachment, of a pre-synthesized probe or by synthesis of the probe on the substrate) on the substrate or chips in lanes stretching across the chip and separated, and these lanes are in turned arranged in blocks of preferably five lanes, although blocks of other sizes will have useful application. The present invention provides individual probes, sets of probes, and arrays of probe sets on chips, in specific patterns which are used to characterize the substances in a complex mixture by producing a distinct image which is representative of the binding interactions between the probes on the chip and the substances in the complex mixture. The pattern of hybridization to the chip allows inferences to be drawn about the substances present in the complex mixture.

The substances in the complex solution will bind to the nucleic acids on the array. The substances of the complex mixture which bind to the nucleic acids of the array may include, but are not limited to, complementary nucleic acids, non-complementary nucleic acids, proteins, antibodies, oligosaccharides, etc. The types of binding may include, but are not limited to, specific and non-specific, competitive and non-competitive, allosteric, cooperative, non-cooperative, complementary and non-complementary, etc. For example, the nucleic acids of the array can bind to complementary nucleic acids in the complex mixture but can also bind in a tertiary manner, independent of base pairing, to non-complementary nucleic acids.

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The nucleic acids of the array or the substances of the complex mixture may be tagged with a detectable label. The detectable label can be, for example, a luminescent label, a light scattering label or a radioactive label. Accordingly, locations at which substances interact can be identified by either determining if the signal of the label has been quenched by binding or identifying locations where the signal of the label is present in cases where the substances of the complex mixture have been labeled. Based on the locations where binding is detected, information regarding the complex mixture can be obtained.

The methods of this invention will find particular use wherever high through-put of samples is required. In particular, this invention is useful in ligand screening settings and for determining the composition of complex mixtures.

Polypeptides are an exemplary system for exploring the relationship between structure and function in biology. When the twenty naturally occurring amino acids are condensed into a polymeric molecule they form a wide variety of three-dimensional configurations, each resulting from a particular amino acid sequence and solvent condition. For example, the number of possible polypeptide configurations using the twenty naturally occurring amino acids for a polymer five amino acids long is over three million. Typical proteins are more than one-hundred amino acids in length.

In typical applications, a complex solution containing one or more substances to be characterized contacts a polymer array comprising polypeptides. The polypeptides of the invention can be prepared by classical methods known in the art, for example, by using standard solid phase techniques. The standard methods include exclusive solid phase synthesis, partial solid phase synthesis methods, fragment condensation, classical solution synthesis and recombinant DNA technology (see Merrifield, (1963) Am. Chem. Soc. 85, 2149-2152). On solid phase, the synthesis is typically commenced from the C-terminal end of the peptide using an alpha-amino protected resin. A suitable starting material can be prepared, for instance, by attaching the required alpha-amino acid to a chloromethylated resin, a hydroxy-methyl resin or a benzhydrylamine resin.

The alpha-amino protecting groups are those known to be useful in the art of stepwise

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synthesis of peptides. Included are acyl type protecting groups, aromatic urethane type protecting groups, aliphatic urethane protecting groups and alkyl type protecting groups. The side chain protecting group remains intact during coupling and is not split off during the deprotection of the amino-terminus protecting group or during coupling. The side chain protecting group must be removable upon the completion of the synthesis of the final peptide and under reaction conditions that will not alter the target peptide.

After removal of the alpha-amino protecting group, the remaining protected amino acids are coupled stepwise in the desired order. An excess of each protected amino acid is generally used with an appropriate carboxyl group activator such as dicyclohexylcarbodiimide (DCC) in solution, for example, in methylene chloride, dimethyl formamide (DMF) mixtures.

These procedures can also be used to synthesize peptides in which amino acids other than the twenty naturally occurring, genetically encoded amino acids are substituted at one, two, or more positions of any of the compounds of the invention. For instance, naphthylalanine can be substituted for tryptophan, facilitating synthesis. Other synthetic amino acids that can be substituted into the peptides of the present invention include L-hydroxypropyl, L-3, 4-dihydroxyphenylalanyl, d-amino acids such as L-d-hydroxylysyl and D-d-methylalanyl, L- α -methylalanyl and β -amino acids non-naturally occurring synthetic amino acids can also be incorporated into the peptides of the present invention (see Roberts *et al.*, (1983) Peptide Synthesis 5, 341-449).

One can replace the naturally occurring side chains of the twenty genetically encoded amino acids (or D amino acids) with other side chains, for instance with groups such as alkyl, lower alkyl, cyclic four, five, six, to seven-membered alkyl, amide, amide lower alkyl, amide di(lower alkyl), lower alkoxy, hydroxy, carboxy and the lower ester derivatives thereof, and with four, five, six, to seven-membered heterocyclic. In particular, proline analogs in which the ring size of the proline residue is changed from five members to four, six or seven members can be employed. Cyclic groups can be saturated or unsaturated, and if unsaturated, can be aromatic or non-aromatic. Heterocyclic groups preferably contain one or more

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nitrogen, oxygen, and/or sulphur heteroatoms. Examples of such groups include the furazanyl, furyl, imidazolidinyl, imidazolyl, imidazolinyl, isothiazolyl, isoxazolyl, morpholinyl, oxazolyl, piperazinyl, piperidyl, pyranyl, pyrazolyl, pyrazolidinyl, pyrazolidinyl, pyrazolyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, thiadiazolyl, thiazolyl, thiomorpholinyl and triazolyl. These heterocyclic groups can be substituted or unsubstituted. Where a group is substituted, the substituent can be alkyl, alkoxy, halogen, oxygen, or substituted or unsubstituted phenyl.

One can also readily modify the peptides of the instant invention by phosphorylation (see Bannwarth et al., (1996) Biorg. Med. Chem. Let. 6, 2141-2146) and other methods for making peptide derivatives of the compounds of the present invention are described in Hruby et al., (1990) Biochem. J. 268, 249-262). Thus, the peptide compounds of the invention also serve as a basis to prepare peptide mimetics with similar biological activity. The array can also comprise peptide mimetics with the same or similar desired biological activity as the corresponding peptide compound but with more favorable activity than the peptide with respect to solubility, stability, and susceptibility to hydrolysis and proteolysis (see Morgan et al., (1989) Ann. Rep. Med. Chem. 24, 243-252).

Peptides suitable for use in this embodiment generally include those peptides, for example, ligands, that bind to a receptor, such as seven transmembrane proteins. Such peptides typically comprise about 150 amino acid residues or less and, more preferably, about 100 amino acid residues or less.

The peptides of the present invention may exist in a cyclized form with an intramolecular disulfide bond between the thiol groups of the cysteines. Alternatively, an intermolecular disulfide bond between the thiol groups of the cysteines can be produced to yield a dimeric (or higher oligomeric) compound. One or more of the cysteine residues may also be substituted with a homocysteine. Other embodiments of this invention provide for analogs of these disulfide derivatives in which one of the sulfurs has been replaced by a CH2 group or other isostere for sulfur. These analogs can be made via an intramolecular or intermolecular displacement, using methods known in the art.

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H. Methods to Identify Agents that Modulate Expression of DORs.

Another embodiment of the present invention provides methods for identifying agents that modulate the expression of a nucleic acid encoding any one of the DOR proteins of the invention such as any protein having the amino acid sequence depicted in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96 and 98. Such assays may utilize any available means of monitoring for changes in the expression level of the nucleic acids of the invention. As used herein, an agent is said to modulate the expression of a nucleic acid of the invention, for instance a nucleic acid encoding any one of the proteins having the amino acid sequence depicted in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96 and 98, if it is capable of up- or down-regulating expression of the nucleic acid in a cell.

In one assay format, cell lines that contain reporter gene fusions between the open reading frame of any one of the nucleotides depicted in SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95 and 97 and any assay fusion partner may be prepared. Numerous assay fusion partners are known and readily available including the firefly luciferase gene and the gene encoding chloramphenicol acetyltransferase (Alam *et al.*, (1990) Anal. Biochem. 188, 245-254). Cell lines containing the reporter gene fusions are then exposed to the agent to be tested under appropriate conditions and time. Differential expression of the reporter gene between samples exposed to the agent and control samples identifies agents which modulate the expression of a nucleic acid encoding at least one of the proteins having the sequence depicted in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96 and 98.

Additional assay formats may be used to monitor the ability of the agent to modulate the expression of a nucleic acid encoding at least one protein of the invention selected from

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the group of proteins having SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96 and 98. For instance, mRNA expression may be monitored directly by hybridization to the nucleic acids of the invention. Cell lines are exposed to the agent to be tested under appropriate conditions and time and total RNA or mRNA is isolated by standard procedures such those disclosed in Sambrook *et al.*, (1985) Molecular Cloning - A Laboratory Manual, Cold Spring Harbor Laboratory Press.

Probes to detect differences in RNA expression levels between cells exposed to the agent and control cells may be prepared from the nucleic acids of the invention. It is preferable, but not necessary, to design probes which hybridize only with target nucleic acids under conditions of high stringency. Only highly complementary nucleic acid hybrids form under conditions of high stringency. Accordingly, the stringency of the assay conditions determines the amount of complementary nucleotides which should exist between two nucleic acid strands in order to form a hybrid. Stringency should be chosen to maximize the difference in stability between the probe:target hybrid and potential probe:non-target hybrids.

Probes may be designed from the nucleic acids of the invention through methods known in the art. For instance, the G+C content of the probe and the probe length can affect probe binding to its target sequence. Methods to optimize probe specificity are commonly available in Sambrook et al., (1985) Molecular Cloning - A Laboratory Manual, Cold Spring Harbor Laboratory Press; or Ausubel et al., (1995) Current Protocols in Molecular Biology, Greene Publishing Company.

Hybridization conditions are modified using known methods, such as those described by Sambrook et al., (1985) and Ausubel et al., (1995) as required for each probe. Hybridization of total cellular RNA or RNA enriched for polyA+RNA can be accomplished in any available format. For instance, total cellular RNA or RNA enriched for polyA RNA can be affixed to a solid support and the solid support exposed to at least one probe comprising at least one, or part of one of the sequences of the invention under conditions in which the probe will specifically hybridize. Alternatively, nucleic acid fragments comprising

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at least one, or part of one of the sequences of the invention can be affixed to a solid support, such as a porous glass wafer. The glass wafer can then be exposed to total cellular RNA or polyA RNA from a sample under conditions in which the affixed sequences will specifically hybridize. Such glass wafers and hybridization methods are widely available, for example, those disclosed by Beattie (WO 95/11755). By examining for the ability of a given probe to specifically hybridize to an RNA sample from an untreated cell population and from a cell population exposed to the agent, agents which up- or down-regulate the expression of a nucleic acid encoding at least one protein having the amino acid sequence depicted in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96 and 98 are identified.

Hybridization for qualitative and quantitative analysis of mRNA may also be carried out by using a RNase Protection Assay (i.e., RPA, see Ma et al., (1996) Methods 10, 273-238). Briefly, an expression vehicle comprising cDNA encoding the gene product and a phage specific DNA dependent RNA polymerase promoter (e.g., T7, T3 or SP6 RNA polymerase) is linearized at the 3' end of the cDNA molecule, downstream from the phage promoter, wherein such a linearized molecule is subsequently used as a template for synthesis of a labeled antisense transcript of the cDNA by in vitro transcription. The labeled transcript is then hybridized to a mixture of isolated RNA (i.e., total or fractionated mRNA) by incubation at 45°C overnight in a buffer comprising 80% formamide, 40 mM Pipes, pH 6.4, 0.4 M NaCl and 1 mM EDTA. The resulting hybrids are then digested in a buffer comprising 40 μg/ml ribonuclease A and 2 μg/ml ribonuclease. After deactivation and extraction of extraneous proteins, the samples are loaded onto urea-polyacrylamide gels for analysis.

In another assay format, agents which effect the expression of the instant gene products, cells or cell lines would first be identified which express said gene products physiologically. Cells and cell lines so identified would be expected to comprise the necessary cellular machinery such that the fidelity of modulation of the transcriptional apparatus is maintained with regard to exogenous contact of agent with appropriate surface

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transduction mechanisms and the cytosolic cascades. Further, such cells or cell lines would be transduced or transfected with an expression vehicle (e.g., a plasmid or viral vector) construct comprising an operable non-translated 5'-promoter containing end of the structural gene encoding the instant gene products fused to one or more antigenic fragments, which are peculiar to the instant gene products, wherein said fragments are under the transcriptional control of said promoter and are expressed as polypeptides whose molecular weight can be distinguished from the naturally occurring polypeptides or may further comprise an immunologically distinct tag. Such a process is well known in the art (see Maniatis et al., (1982) Molecular Cloning - A Laboratory Manual, Cold Spring Harbor Laboratory Press).

Cells or cell lines transduced or transfected as outlined above would then be contacted with agents under appropriate conditions; for example, the agent comprises an acceptable excipient and is contacted with cells comprised in an aqueous physiological buffer such as phosphate buffered saline (PBS) at physiological pH, Eagles balanced salt solution (BSS) at physiological pH, PBS or BSS comprising serum or conditioned media comprising PBS or BSS and/or serum incubated at 37°C. Said conditions may be modulated as deemed necessary by one of skill in the art. Subsequent to contacting the cells with the agent, said cells will be disrupted and the polypeptides from disrupted cells are fractionated such that a polypeptide fraction is pooled and contacted with an antibody to be further processed by immunological assay (e.g., ELISA, immunoprecipitation or Western blot). The pool of proteins isolated from the "agent contacted" sample will be compared with a control sample where only the excipient is contacted with the cells and an increase or decrease in the immunologically generated signal from the "agent contacted" sample compared to the control will be used to distinguish the effectiveness of the agent.

I. Methods to Identify Agents that Modulate Activity of DORs

Another embodiment of the present invention provides methods for identifying agents that modulate at least one activity of a protein of the invention such as any one of the proteins having the amino acid sequence of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26,

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28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96 and 98. Such methods or assays may utilize any means of monitoring or detecting the desired activity.

In one format, the relative amounts of a protein of the invention between a cell population that has been exposed to the agent to be tested compared to an un-exposed control cell population may be assayed. In this format, probes such as specific antibodies are used to monitor the differential expression of the protein in the different cell populations. Cell lines or populations are exposed to the agent to be tested under appropriate conditions and time. Cellular lysates may be prepared from the exposed cell line or population and a control, unexposed cell line or population. The cellular lysates are then analyzed with the probe.

Antibody probes are prepared by immunizing suitable mammalian hosts in appropriate immunization protocols using the peptides, polypeptides or proteins of the invention if they are of sufficient length, or if desired, required to enhance immunogenicity, conjugated to suitable carriers. Methods for preparing immunogenic conjugates with carriers such as BSA, KLH, or other carrier proteins are well known in the art. In some circumstances, direct conjugation using, for example, carbodiimide reagents may be effective; in other instances linking reagents such as those supplied by Pierce Chemical Co., may be desirable to provide accessibility to the hapten. The hapten peptides can be extended at either the amino or carboxy terminus with a cysteine residue or interspersed with cysteine residues, for example, to facilitate linking to a carrier. Administration of the immunogens is conducted generally by injection over a suitable time period and with use of suitable adjuvants, as is generally understood in the art. During the immunization schedule, titers of antibodies are taken to determine adequacy of antibody formation.

While the polyclonal antisera produced in this way may be satisfactory for some applications, for some applications, use of monoclonal preparations is preferred. Immortalized cell lines which secrete the desired monoclonal antibodies may be prepared using the standard method of Kohler & Milstein, (1975) Nature 256, 495-497 or modifications which effect immortalization of lymphocytes or spleen cells, as is generally known. The

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immortalized cell lines secreting the desired antibodies are screened by immunoassay in which the antigen is the peptide hapten, polypeptide or protein. When the appropriate immortalized cell culture secreting the desired antibody is identified, the cells can be cultured either in vitro or by production in ascites fluid.

The desired monoclonal antibodies are then recovered from the culture supernatant or from the ascites supernatant. Fragments of the monoclonal or polyclonal antisera which contain the immunologically significant portion can be used as antagonists, as well as the intact antibodies. Use of immunologically reactive fragments, such as the Fab, Fab' of F(ab')₂ fragments is often preferable, as these fragments are generally less immunogenic than the whole immunoglobulin.

The antibodies or fragments may also be produced, using current technology, by recombinant means. Antibody regions that bind specifically to the desired regions of the protein can also be produced in the context of chimeras with multiple species origin, particularly humanized antibodies.

Agents that are assayed in the above method can be randomly selected or rationally selected or designed. As used herein, an agent is said to be randomly selected when the agent is chosen randomly without considering the specific sequences involved in the association of the a protein of the invention alone or with its associated substrates, binding partners, etc. An example of randomly selected agents is the use a chemical library or a peptide combinatorial library, or a growth broth of an organism.

As used herein, an agent is said to be rationally selected or designed when the agent is chosen on a non-random basis which takes into account the sequence of the target site and its conformation in connection with the agent's action. Agents can be rationally selected or rationally designed by utilizing the peptide sequences to identify proposed binding motifs, glycosylation and phosphorylation sites on the protein.

The agents of the present invention can be, as examples, peptides, small molecules, vitamin derivatives, as well as carbohydrates. A skilled artisan can readily recognize that there is no limit as to the structural nature of the agents of the present invention. Dominant-

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negative proteins, DNA encoding these proteins, antibodies to these proteins, peptide fragments of these proteins or mimics of these proteins may be contacted with cells to affect function. "Mimic" as used herein refers to the modification of a region or several regions of a peptide molecule to provide a structure chemically different from the parent peptide but topographically and functionally similar to the parent peptide (see Meyers, (1995) Molecular Biology & Biotechnology, VCH Publishers).

The peptide agents of the invention can be prepared using standard solid phase (or solution phase) peptide synthesis methods, as is known in the art. In addition, the DNA encoding these peptides may be synthesized using commercially available oligonucleotide synthesis instrumentation and produced recombinantly using standard recombinant production systems. The production using solid phase peptide synthesis is necessitated if non-geneencoded amino acids are to be included.

Another class of agents of the present invention are antibodies immunoreactive with critical positions of proteins of the invention. Antibody agents are obtained by immunization of suitable mammalian subjects with peptides, containing as antigenic regions, those portions of the protein intended to be targeted by the antibodies.

J. Transgenic Organisms

Transgenic insects containing mutant, knock-out or modified genes corresponding to any one of the cDNA sequences depicted in SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95 and 97 are also included in the invention. Transgenic insects are genetically modified insects into which recombinant, exogenous or cloned genetic material has been experimentally transferred. Such genetic material is often referred to as a "transgene". The nucleic acid sequence of the transgene, in this case a form of any one of the sequences depicted in SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95 and 97, may be integrated either at a locus of a genome

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where that particular nucleic acid sequence is not otherwise normally found or at the normal locus for the transgene. The transgene may consist of nucleic acid sequences derived from the genome of the same species or of a different species than the species of the target insect.

The term "germ cell line transgenic insect" refers to a transgenic insect in which the genetic alteration or genetic information was introduced into a germ line cell, thereby conferring the ability of the transgenic insect to transfer the genetic information to offspring. If such offspring in fact possess some or all of that alteration or genetic information, then they too are transgenic insects.

The alteration or genetic information may be foreign to the species of insect to which the recipient belongs, foreign only to the particular individual recipient, or may be genetic information already possessed by the recipient. In the last case, the altered or introduced gene may be expressed (i.e., over-expression and knock-out) differently than the native gene.

Transgenic insects can be produced by a variety of different methods including P element-mediated transformation by microinjection (see, e.g., Rubin & Spradling, (1982) Science 218, 348-353; Orr & Sohal, (1993) Arch. Biochem. Biophys. 301, 34-40), transformation by microinjection followed by transgene mobilization (Mockett et al., (1999) Arch. Biochem. Biophys. 371, 260-269), electroporation (Huynh & Zieler, (1999) J. Mol. Biol. 288, 13-20) and through the use of baculovirus (Yamao et al., (1999) Genes Dev. 13, 511-516. Furthermore, the use of adenoviral vectors to direct expression of a foreign gene to olfactory neuronal cells can also be used to generate transgenic insects (see, e.g., Holtmaat et al., (1996) Brain. Res. Mol. Brain Res. 41, 148-156).

A number of recombinant or transgenic insects have been produced, including those which over-express superoxide dismutase (Mockett et al., (1999) Arch. Biochem. Biophys. 371, 260-269); express Syrian hamster prion protein (Raeber et al., (1995) Mech. Dev. 51, 317-327); express cell-cycle inhibitory peptide aptamers (Kolonin & Finley (1998) Proc. Natl. Acad. Sci. USA 95, 14266-14271); and those which lack expression of the putative ribosomal protein S3A gene (Reynaud et al., (1997) Mol. Gen. Genet. 256, 462-467).

While insects remain the preferred choice for most transgenic experimentation, in

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some instances it is preferable or even necessary to use alternative animal species.

Transgenic procedures have been successfully utilized in a variety of animals, including mice, rats, sheep, goats, pigs, dogs, cats, monkeys, chimpanzees, hamsters, rabbits, cows and guinea pigs (see, e.g., Kim et al., (1997) Mol. Reprod. Dev. 46, 515-526; Houdebine, (1995)

Reprod. Nutr. Dev. 35, 609-617; Petters, (1994) Reprod. Fertil. Dev. 6, 643-645; Schnieke et al., (1997) Science 278, 2130-2133; and Amoah, (1997) J. Anim. Sci. 75, 578-585).

The method of introduction of nucleic acid fragments into insect cells can be by any method which favors co-transformation of multiple nucleic acid molecules. For instance, Drosophila embryonic Schneider line 2 (S2) cells can be stably transfected as previously described (Schneider, (1972) J. Embryol. Exp. Morphol. 27, 353-365). Detailed procedures for producing transgenic insects are readily available to one skilled in the art (see Rubin & Spradling, (1982) Science 218, 348-353; Orr & Sohal, (1993) Arch. Biochem. Biophys. 301, 34-40. herein incorporated by reference in their entirety).

K. Uses for Agents that Modulate at Least One Activity of DORs

1. Introduction.

Organisms, including insects, are continually exposed to a great number of volatiles released by other organisms as well as by other aspects of their environment. The olfactory receptor genes of the present invention play an important role in the detection and processing of these chemical stimuli, some of which have been implicated in initiating and modulating host-seeking and other behaviors, such as mating behaviors (see, for example, Roth, (1951) Ann. Entomol. Soc. Am. 44, 59-74; Jones et al., (1976) Ent. Exp. Appn. 19, 19-22; Gillies, (1980) Bull. Ent. Res. 70, 525-532; Kline et al., (1991) J. Med. Entomol. 28, 254-258). For a recent, thorough review of the many practical applications of the present invention (see Karg & Suckling, (1999) Applied aspects of insect olfaction, in: Hansson (ed.), Insect Olfaction, Springer, which is incorporated by reference in its entirety).

Most importantly, the DOR genes of the present invention may be used to track down odor receptor genes in insects that damage crops or transmit diseases. The present invention

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provides the tools and methodologies for finding specific compounds that interfere with the insects' ability to detect odors.

Of course, the present invention has important implications for improved methods of using pheromones and other semiochemicals for pest control. In addition, recent advancements in many other fields have greatly increased the variety of additional technologies for which the present invention also has significant applications. Examples of such'advancements include, but are not limited to the following: i) the development and application of new techniques of chemical identification and synthesis; ii) new chemical release techniques; iii) more sophisticated application technologies; and iv) more detailed information about the behavior of specific organisms.

While not wishing to be bound by the specific embodiments discussed herein, the following sections provide an overview of the wide variety of applications for which the present invention may be employed.

2. Definitions.

As used herein, the term "allomones" refers to any chemical substance produced or acquired by an organism that, when it contacts an individual of another species, evokes in the receiver a behavioral or developmental reaction adaptively favorable to the transmitter.

As used herein, the term "host" refers to any organism on which another organism depends for some life function. Examples of hosts include, but are not limited to, humans which may serve as a host for the feeding of certain species of mosquito and the leaves of soybeans (Glycine max(L.)) which may act as hosts for the oviposit of the green cloverworm (Plathypena scabra (F.)).

As used herein, the term "kairomones" refers to any of a heterogeneous group of chemical messengers that are emitted by organisms of one species but benefit members of another species. Examples include, but are not limited to, attractants, phagostimulants, and other substances that mediate the positive responses of, for example, predators to their prey, herbivores to their food plants, and parasites to their hosts. Kairomones suitable for the purposes of the invention and methods of obtaining them are described, for example, Science

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(1966) 154, 1392-93; Hedin, (1985) Bioregulators for Pest Control, American Chemical Society, Washington, 353-366.

As used herein, the term "pheromone" refers to a substance, or characteristic mixture of substances, that is secreted and released by an organism and detected by a second organism of the same or a closely related species, in which it causes a specific reaction, such as a definite behavioral reaction or a developmental process. Examples include, but are not limited to, the mating pheromones of fungi and insects. More than a thousand moth sex pheromones (Toth et al., (1992) J. Chem. Ecol. 18, 13-25; Am et al., (1998) Appl. Entomol. Zoo. 33, 507-511) and hundreds of other pheromones have now been identified, including aggregation pheromones from beetles and other groups of insects. Various compositions, including resins and composite polymer dispensers, have been developed for the controlled release of pheromones have been developed (see, e.g., U.S. Patent No. 5,750,129 & 5,504,142).

As used herein, the term "semiochemical" refers to any chemical substance that delivers a message or signal from one organism to another. Examples of such chemicals include, but are not limited to, pheromones, kairomones, oviposition deterrents, or stimulants, and a wide range of other classes of chemicals (see, for example, Nordlund, (1981) Semiochemicals: A review of the terminology, in: Nordlund et al., (ed.) Semiochemicals: Their Role in Pest Control, John Wiley; Howse et al., (1998) Insect Pheromones and Their Use in Pest Management, Chapman & Hall, London).

As used herein, the term "synomones" refers to any chemical substance which benefits both the emitter and receiver. Examples include, but are not limited to, compounds involved in floral attraction of pollinators and species-isolating mechanisms, such as sex pheromones of related species, where an inhibitor often functions to prevent mating among sympatric species.

As used herein, the term "volatile" refers to a chemical which evaporates readily at those temperatures and pressures which are considered the relevant temperatures and pressures for the reference organism of interest.

3. As Tools for Further Scientific Research.

Identification of Olfactory Receptor Genes in Other Organisms. The algorithms of the

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present invention may be used directly to search for olfactory receptor genes in other organisms, as explained elsewhere herein.

Alternatively, nucleic acid probes or primers may be designed based on the DOR genes of the present invention. Such probes or primers may be used to identify and isolate olfactory receptor genes in other organisms. Methods of creating and using the necessary nucleic acid probes and primers are discussed elsewhere herein.

The highest probability of success in locating olfactory genes in other organisms using the DOR genes of the present invention will most likely occur by using a boot-strapping or leap-frogging method. Such methods involve first probing organisms most related to fruit flies and successively progressing to more unrelated organisms, using the most newly identified olfactory receptor genes to identify similar genes in the next, more unrelated, insect of interest. Thus, the first organisms to probe with the DOR genes of the present invention most preferably may be other flies from the order Diptera (i.e., the two-winged or true flies). Examples of suitable flies include, but are not limited to, the tsetse fly, horse fly, house fly, bluebottle fly, hover fly and mosquito. Dipterans which transmit diseases causing serious health problems are of particular interest (e.g., horse fly, tsetse fly, mosquito).

After the identification of olfactory receptor genes in various *Diptera* insects, the next organisms to probe most preferably may be from orders within the same subclass as *Diptera*. Finally, the next insects to use would be those from orders not within the same subclass as *Diptera*.

The insects which cause substantial health risks, crop damage, or other significant damage (e.g., to housing structure or cotton clothing) may be the most desirable targets for such studies. Examples of such insects include, but are not limited to, green cloverworm, Mexican bean beetle, potato leafhopper, corn earworm, green stink bug, northern corn rootworm, western corn rootworm, cutworms, wireworms, thrips, fleas, aphids (e.g., pea aphid, spotted alfalfa aphid), European corn borer, fall armyworm, southwestern corn borer, grasshoppers, Japanese beetle, termites, leafhoppers (e.g., potato leafhopper, three-cornered alfalfa hopper), stink bugs, crickets, Hessian fly, greenbugs and weevils (e.g., alfalfa weevil,

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bollweevil).

Olfactory receptor genes identified by this process may then be used to screen non-Insecta organisms for olfactory receptor genes. Organisms of interest may include, but be limited to, mites, ticks, spiders, nematodes, centipedes, mice, rats, salmon, pigeons, dogs, horses and humans.

Genetic Manipulations. The tools and methodologies of the present invention may be used by neurobiologists to probe more complex workings of an organism's response system, including those of a mammal's brain.

Knock-outs. By systematically knocking out the olfactory receptor genes of the present invention and observing the effects on odor sensitivity and behavior, researchers will be able to piece together a wiring diagram of the olfactory system of the fruit fly.

The term "knock-out" generally refers to mutant organisms which contain a null allele of a specific gene. Methods of making knock-out or disruption transgenic animals, especially mice, are generally known by those skilled in the art and are discussed herein and elsewhere (see, for example, the section herein entitled Transgenic Organisms and the following: Manipulating the Mouse Embryo, (1986) Cold Spring Harbor Laboratory Press; Capecchi, (1989) Science 244, 1288-1292; Li et al., (1995) Cell 80, 401-411; U.S. Patent No. 5,981,830 & 5,789,654, each of which is incorporated herein by reference.

Parallel studies may be conducted in other organisms by using the olfactory receptor genes and the methods of the present invention to identify the olfactory receptor genes of other organisms and then creating knock-outs for the olfactory receptor genes of those organisms.

Disabling Genes. Using the olfactory receptor genes of the present invention, it is now possible to selectively disable specific DOR genes and look for changes in odor response and behavior. Parallel studies may be conducted in other organisms by using the olfactory receptor genes and the methods of the present invention to identify the olfactory receptor genes of other organisms and then disabling olfactory receptor genes of those organisms.

Methods of disabling genes are generally known by those skilled in the art. An

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example of an effective disabling modification would be a single nucleotide deletion occurring at the beginning of a olfactory receptor gene that would produce a translational reading frameshift. Such a frameshift would disable the gene, resulting in non-expressible gene product and thereby disrupting functional protein production by that gene. Protease production by the gene could be disrupted if the regulatory regions or the coding regions of the protease genes are disrupted.

In addition to disabling genes by deleting nucleotides, causing a transitional reading frameshift, disabling modifications would also be possible by other techniques including insertions, substitutions, inversions or transversions of nucleotides within the gene's DNA that would effectively prevent the formation of the protein coded for by the DNA.

It is also within the capabilities of one skilled in the art to disable genes by the use of less specific methods. Examples of less specific methods would be the use of chemical mutagens such as hydroxylamine or nitrosoguanidine or the use of radiation mutagens such as gamma radiation or ultraviolet radiation to randomly mutate genes, such as the DOR genes of the present invention. Such mutated strains could, by chance, contain disabled olfactory receptor genes such that the genes are no longer capable of producing functional proteins for any one or more of the domains. The presence of the desired disabled genes could be detected by routine screening techniques. For further guidance, see U.S. Patent No. 5,759,538.

Over-expression. Using the olfactory receptor genes of the present invention, it is now possible to selectively over-express specific DOR genes and look for changes in odor response and behavior. Parallel studies may be conducted in other organisms by using the olfactory receptor genes and the methods of the present invention to identify the olfactory receptor genes of other organisms and then overexpress the olfactory receptor genes of those organisms.

Methods of overexpressing genes are generally known by those skilled in the art. For examples of producing cells which overexpress specific genes, see, for example, U.S. Patent Numbers 5,905,146; 5,849,999; 5,859,311; 5,602,309; 5,952,169 and 5,772,997 (HER2 receptor).

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Modulating or Inhibiting Expression. Using the olfactory receptor genes of the present invention, it is now possible to selectively modulate or inhibit specific DOR genes using antisense oligomers which specifically hybridize with the DNA or RNA encoding the DOR genes. One skilled in the art could so modulate or inhibit the expression of the DOR genes and detect for changes in odor response and behavior. Parallel studies may be conducted in other organisms by using the olfactory receptor genes and the methods of the present invention to identify the olfactory receptor genes in other organisms and then use antisense oligers to the olfactory receptor genes of those organisms. Methods for inhibiting expression of genes, especially genes coding for receptor genes, using antisense constructs, including generation of antisense sequences in situ are described, for example, in U.S. Patent Numbers 5,856,099; 5,556,956; 5,716,846; 5,135,917 and 6,004,814.

Other methods that can be used to inhibit expression of an endogenous gene are applicable to the present invention. For example, formation of a triple helix at an essential region of a duplex gene serves this purpose. The triplex code, permitting design of the proper single stranded participant is also known in the art. (See H. E. Moser, et al., (1987) Science 238: 645-650 and M. Cooney, et al., (1988) Science 241: 456-459). Regions in the control sequences containing stretches of purine bases are particularly attractive targets. Triple helix formation along with photocrosslinking is described, e.g., in Praseuth et al., (1988) Proc. Natl Acad. Sci. USA 85:1349-1353.

Studying Behavior. The present invention is useful for studying the developmental aspects of the olfactory receptor genes which appear to be active at different times during development. Such studies may help organize the olfactory systems in various organisms and may help explain the behavior of various organisms.

The tools and methodologies of the present invention may be used to study the influence of environmental conditions on pheromone communication. For example, newly identified olfactory receptor genes may be used to study the effects of different rearing temperatures and light regimes (selected to mimic those occurring in the spring and summer growing seasons) on the response of various *Lepidoptera* insects, such as the cabbage looper

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moth (*Trichoplusia ni* (Hubner)). For a description of the methods which might be used for such a study, see, for example, Grant *et al.*, (1996) Physiol. Entomol. 21, 59-63.

4. For Organism Detection, Monitoring and Control.

General Pest Management. The olfactory receptor genes identified herein and identified using the methods of the present invention may be used to identify compounds which may be used for pest management. It is especially desirable to utilize various aspects of the present invention for pest management related to crop protection.

The application of pheromones is now firmly established as a key component of pest management and control, especially within the framework of integrated pest management (IPM). An object of organism control is to modulate an organism's behavior or activity so as to reduce the irritation, sickness, or death of the host (e.g., a plant host), or to decrease the general health and proliferation of the organism.

For example, the propagation of a mouse population in a given area of actual or potential mice infestation may be prevented or inhibited by treating such an area with an effective amount of male mouse pheromones, wherein such pheromones have male mouse aversion signaling properties (see, e.g., U.S. Patent No. 5,252,326).

Insect Repellents and Insecticides. The present invention provides the tools and methodologies useful for identifying compounds which modulate insect behavior by exploiting the sensory capabilities of the target insect. For example, attempts have been made to describe and synthesize the complex interactions which underlie host-seeking behavior in mosquitoes. Using the methods and olfactory receptor genes of the present invention, it is possible to design specific compounds which target mosquito olfactory receptor genes. Thus, the present invention provides the ability to alter or to eliminate the orientation and feeding behaviors of mosquitoes and thereby have a positive impact on world health by controlling mosquito-borne diseases, such as malaria.

Mosquito olfactory receptor genes may be identified and/or targeted using various aspects of the present invention. For example, the olfactory receptor genes of the present invention may be used to design probes as discussed elsewhere herein for the identification

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and characterization of mosquito olfactory receptor genes. Alternatively, the algorithm of the present invention may be used to identify mosquito olfactory receptor genes in the genetic databases for mosquitoes. Once the mosquito olfactory receptor genes are identified, then various screening methods described elsewhere herein, such as the high throughput assays discussed elsewhere herein, may be used to identify synthetic and natural compounds which may modulate the behavior of the insect.

Mating Enhancement and Disruption. The olfactory receptor genes identified herein and identified using the methods of the present invention may be used to identify compounds which interfere with the orientation and mating of a wide range of organisms, including insects. Thus, the present invention enables the identification of compositions which disrupt insect mating by selective inhibition of specific receptor genes involved in mating attraction (see, e.g., U.S. Patent No. 5,064,820).

Animal Repellants. The olfactory receptor genes identified herein and identified using the methods of the present invention may be used to identify compounds which may be used as animal repellants. Such compositions may be used to repel both predatory and non-predatory animals (see, e.g., U.S. Patent No. 4,668,455).

6. Organism Attraction.

<u>Insect Attractants</u>. The olfactory receptor genes identified herein and identified using the methods of the present invention may be used to identify compounds which attract specific insects to a particular location (see, e.g., U.S. Patent No. 4,880,624 & 4,851,218).

For example, aspects of the present invention may to used in various methods which reduce or eliminate the levels of particular insect pests, such as mosquitoes and tsetse flies.

As a particular example, insect traps can be created wherein the pheromone attracts a particular insect, like the tsetse fly, and the insect so attracted dies in the trap. In this way, the population of tsetse flies may be reduced or eliminated in a particular area.

The insect attractant compositions so identified may also be combined with an insecticide, for example as an insect bait in microencapsulated form. Alternatively, or in addition, the insect attractant composition may be placed inside an insect trap, or in the

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vicinity of the entrance to an insect trap.

In addition to killing insects, the trapping of insects is often very important for estimating or calculating how many insects of a particular type are feeding within a specific area. Such estimates are used to determine where and when insecticide spraying should be commenced and terminated.

Insect traps which may be used are, for example, those as described in PCT/BG93/01442 and U.S. Patent No. 5,713,153. Specific examples of insect traps include, but are not limited to, the Gypsy Moth Delta Trap®, Boll Weevil Scout Trap®, Jackson trap, Japanese beetle trap, McPhail trap, Pherocon 1C trap, Pherocon II trap, Perocon AM trap and Trogo trap.

Kairomones may be used as an attractancy for the enhancement of the pollination of selected plant species.

Attractant compositions which demonstrate biological activity toward one sex which is greater than toward the opposite sex may be useful in trapping one sex of a specific organism over another. For example, a composition may be a highly effective attractant for male apple ermine moths (*Yponomeuta malinellus* (Zeller)) and not so effective an attractant for female apple ermine moths. By attracting adult males to field traps, the composition provides a means for detecting, monitoring, and controlling this agricultural pest (see, e.g., U.S. Patent No. 5,380,524).

Attracting Predators and Parasitoids. The olfactory receptor genes of the present invention and the olfactory receptor genes identified using the methods of the present invention may also be used to identify chemicals which attract various predators and parasitoids. Attracting the predators and parasitoids which attack certain pests offers an alternative method of pest management.

Animal Attractants. The olfactory receptor genes identified herein and those identified by the methods of the present invention may be used to identify chemicals which attract household domesticated animals. For example, a pheromone-containing litter preparation may attract the animals and absorb liquids and liquid-containing waste released by the

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attracted animal (see, e.g., U.S. Patent No. 5,415,131).

Synthetic Perfumes. A "perfume" or a "fragrance composition" is a specific pleasantly odorous cosmetic composition for topical application to an individual. The olfactory receptor genes identified herein and those identified by the methods of the present invention may be used to identify chemicals which may be produced and used as synthetic perfumes. Such perfumes may be used to disguise odors or enhance attraction between humans (see, e.g., U.S. Patent No. 5,278,141).

- 7. Pharmaceuticals. The olfactory receptor genes identified herein and those identified using the methods of the present invention may be used to identify pharmaceutical compounds useful for altering the behavior and physiology of animals. Examples of such compounds include, but are not limited to, certain Androstene steroids that effectuate a change in human hypothalamic function (see, e.g., U.S. Patent No. 5,969,168).
- 8. Industrial Applications. The olfactory receptor genes identified by the methods of the present invention may be used for a number of different industrial applications including, but not limited to the following:
- a) Identification of appetite suppressant compounds and using same to suppress and/or control appetite.
 - b) Trapping odors of a specific type.
 - c) As Biosensors.
- Explosive and drug detectors. The detectors may be synthetic, such as biologicallyinspired robotic sensors, or biological sensors, such as sniffing dogs which are especially sensitive to certain odors.
- 2) Population of olfactory receptor genes expressed in cell culture. Olfactory receptor genes can be introduced into a cell line and the transformed cells maintained in culture through multiple generations. By creating specific cell lines which express multiple olfactory genes at once, it would be possible to use such cell cultures to investigate how odorants interact with odorant receptor genes. Thus, the present invention provides methods for identifying odorant fingerprints, wherein such methods include contacting a series of cells

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containing and expressing known odor receptor genes with a desired sample, and determining the type and quantity of the odorant ligands present in the sample (see, e.g., U.S. Patent No. 5,993,778). As discussed elsewhere herein, the interaction of substances with the receptors can be identified using appropriate labels, such as those provided by luciferase, the jellyfish green fluorescent protein (GFP) or β -galactosidase.

- 3) Biochip Arrays. As discussed elsewhere herein, biochip arrays of odorant receptor genes can be generated. The arrays may be used to detect olfactory receptor ligands via an appropriate marker or via a chemical or electrical signal. Arrays may be designed for specific purposes, such as, but not limited to, detecting perfumes, explosives, drugs, pollutants, and toxins.
- d) Training organisms to conduct certain tasks. Examples include, but are not limited to, the following:
- Training mice to pull guide line for stringing fiber optic cable through existing conduit holding copper wire.
- Training mice to find their way through a maze based on smell (see, e.g., Otto et al., (1991) Hippocampus 1, 181-192; Granger et al., (1991) Psych. Science 2, 116-118).
- 3) Improving the orientation and homing performance of pigeons (see, e.g., Wiltschko, (1996) J. Exp. Biol. 199, 113-119) and fish (see, e.g., Cao et al. (1998) Proc. Natl. Acad. Sci. USA 95(20):11987-11992).
- 4) Orient or reorient the behavior of worker bees of a rearing colony by incorporating a composition which includes one or more pheromones which elicits particular bee behavior towards the larvae. Thus, the beekeeper may orient or reorient the bees towards a particular activity such as, but not limited to, inducing improved acceptance of the larvae at the beginning of rearing, to increase the production of royal jelly, regulate the feeding of the larvae as to favor the development of queen bees, etc. (see, e.g., U.S. Patent No. 5,695,383).

Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the following illustrative examples, make and utilize the

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compounds of the present invention and practice the claimed methods. The following working examples therefore, specifically point out the preferred embodiments of the present invention, and are not to be construed as limiting in any way the remainder of the disclosure.

5 EXAMPLES

Example 1: Identification of candidate olfactory receptor genes

In vertebrates and nematodes it is estimated that there are hundreds of olfactory receptor genes, widely distributed in the genome (Buck & Axel, (1991) Cell 65, 175-187; Troemel et al., (1995) Cell 83, 207-218). With approximately 10% of the Drosophila genome sequenced, it was likely that some of the Drosophila odorant receptor genes have been sequenced. A two-step strategy was developed to identify odorant receptor genes from the genomic database. First, a computer algorithm was designed to search the Drosophila genomic sequence for open reading frames (ORFs) from candidate odorant receptor genes. Second, RT-PCR was used to determine if transcripts from any of these ORFs were expressed in olfactory organs. Finally, in situ hybridization was used to localize expression of DOR genes.

Step 1: Computer algorithm for identification of GPCR genes. The algorithm used to identify GPCR genes used statistical characterization of amino acid physico-chemical profiles in combination with a non-parametric discriminant function. The key approach is to use the information in the interplay between the local structure (transmembrane alpha helix) and the global structure (repeated multiple domains) and characterize this information with concise statistical variables. The algorithm was trained on a set of 100 putative GPCR sequences from the GPCR database (GPCRDB) at http://swift.embl-heidelberg.de/7tm and a set of 100 random proteins selected from the SWISSPROT database (this training set was later expanded, but that version was not used for the genes reported in this paper). In the first step, three sets of descriptors were used to summarize the physico-chemical profiles of the sequences. These were GES scale of hydropathy (Engelman et al., (1986) Annu. Rev. Biophys. Biophys. Chem. 15, 321-353), polarity (Brown, (1991) Molecular Biology Labfax,

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Academic Press), and amino acid usage frequency. For the first two of these measurements, a sliding window profile was employed (White, (1994) Membrane Protein Structure, Oxford University Press) using a kernel of 15 amino acid constant function convoluted with a 16 amino acid Gaussian function. These profiles were then summarized with three statistics; the periodicity (characterizing the quasi-periodic presence of the transmembrane domain), average derivative (characterizing the abrupt change between the transmembrane domain and non-transmembrane domain), and the variance of the derivative (also characterizing the abrupt change). GES periodicity, variance of polarity derivative, polarity periodicity and amino acid frequency were used as the four variables and each sequence was therefore characterized by four variables. These four variables were used in a non-parametric linear discriminant function that was then optimized to separate the known GPCRs from random proteins in the training set. The same linear discriminant function with the scores derived from the training set was then used to screen the genomic database for candidate genes. The candidate sequences were given significance values by an odds ratio of the GPCRs and non-GPCRs computed using the observed empirical distribution of the training set. More detailed information about the algorithm is available at http://www.neuron.org/cgi/content/full/22/2/327/dc1.

The computational screens used the genomic sequence data obtained by FTP from the Berkeley *Drosophila* Genome Project (BDGP, http://www.fruitfly.org, version 6/98). First, the ORFs of 300 bases or longer in all six frames were identified. Next, a program written to identify GPCRs statistically by their physico-chemical profile was used to screen for candidate ORFs as described above. The number of possible candidates was reduced by comparing them to *Drosophila* codon usage tables (http://flybase.bio.indiana.edu, version 10). Candidate ORFs whose codon usage differed at a significance level of 0.0005 by the chi-square statistic were discarded from the candidate set. Using these screening steps, 34 candidate ORFs were obtained.

Further analysis revealed that eight of the thirty-four candidate ORFs corresponded to genes of known function, for example a cyclic nucleotide-gated channel (Baumann et al., (1994) EMBO J. 13, 5040-5050) and these ORFs were not further analyzed. Most of the

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remaining ORFs encoded fewer than seven predicted transmembrane domains. The genomic DNA surrounding each of the computer-identified ORFs was therefore examined for the presence of neighboring ORFs encoding additional transmembrane domains to which the original ORFs might be spliced. *Drosophila* 5' and 3' intron-exon consensus splice sequences were used in this analysis to help identify linked exons (Mount *et al.*, (1992) Nucleic Acids Res. 20, 4255-4262). This analysis yielded several genes that encoded seven-transmembrane-domain proteins (22A.1 and 22A.2).

Step 2: Sequence analysis of DOR olfactory genes. To determine if these two candidates were part of a larger family of genes encoding seven-transmembrane-domain proteins, BLAST searches of the *Drosophila* genome database were conducted using the candidate gene sequences to identify related genes (Altschul *et al.*, (1990) J. Mol. Biol. 215, 403-410). The computer algorithms employed identified the ORFs for the second exons of 22A.1 and 22A.2, which encode transmembrane domains 1-4. These ORFs are on the BDGP P1 clone designated DS005342. The DS005342 sequence was examined around the initial ORFs for neighboring ORFs which encoded additional potential transmembrane domains. Key to the identification of these neighboring ORFs was the presence of intron-exon consensus splice sequences: GTRAGT for the 5' end and HAG for the 3' end (Mount *et al.*, (1992) Nucleic Acids Res. 20, 4255-4262). 22A.1 and 22A.2 were found to have two other introns in corresponding locations, all of which had conserved splice sequences.

The amino acid sequences of 22A.1 and 22A.2 were used in searches of the Drosophila genome database using the tBLASTn program of the BDGP. These searches yielded partial sequences of other members of the DOR family. To complete the sequences of these genes, an analysis of the genomic DNA around each identified ORF was carried out as was done for 22A.1 and 22A.2, using the locations of conserved introns in the genes, the intron consensus splice sequences, and the tBLASTn alignments as guides. Use of the genes identified in the second round as query sequences in tBLASTn searches and subsequent similar analysis of genomic DNA yielded the remaining genes. Additional searches of GenBank and SwissProt databases were performed with the NCBI (National Center for

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Biotechnology Information) BLAST network.

The sequence alignment in Figure 3 is based on the alignments predicted by the tBLASTn program of the BDGP but was edited extensively. The 5' splice sequences for the most 3' introns of both 2F.1 and 47E.1 were unfavorable. It was assumed that these introns were spliced nonetheless, as the resulting amino acid sequence displayed greater sequence identity to other DOR family members. If these introns were not spliced out, then the lengths of 2F.1 and 47E.1 would not be significantly altered from the lengths indicated in Figure 3. 2F.1 was independently predicted to be a gene (GenBank accession number 2661571) by the EMBL genefinder program subsequent to the submission of the provisional application to which this application claims priority.

Homologs of the two candidates were found, and their sequences were used in turn for further database searches. In total, forty-nine genes have been identified from the approximately 16% genomic sequence currently available. Applicants have tentatively named this family of genes DOR (for *Drosophila* Olfactory Receptor), and each individual gene was named based upon its cytogenetic location in the genome. Thus the two genes identified initially are DOR22A.1 and DOR22A.2, which were abbreviated here as 22A.1 and 22A.2 (the final digit in this nomenclature is used to distinguish the genes at a site and does not refer to the cytogenetic band number). The genomic locations of all the DOR genes identified so far are indicated in Figure 2A, and an alignment of their amino acid sequences is presented in Figure 3. Of the forty-nine family members, the great majority have been found to be expressed in either the antenna or the maxillary palp, or in both, based upon RT-PCR analysis (Table 1) and *in situ* hybridizations to RNA in tissue sections.

The DOR genes have no significant similarities to any known genes, and do not appear in any of the *Drosophila* EST databases. However, Kyte-Doolittle hydropathy plots of the predicted proteins show that each has approximately seven peaks that could represent transmembrane domains (Figure 2C) (Kyte & Doolittle, (1982) J. Mol. Biol. 157, 105-132). The lengths of the sixteen proteins are between 369 and 403 amino acids, similar to the lengths of most previously described families of GPCRs (Probst *et al.*, (1992) DNA Cell Biol.

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11, 1-20). In addition, the spacing of the putative transmembrane domains gives rise to predicted intracellular and extracellular loops similar in size to those in many families of GPCRs (Probst et al., (1992) DNA Cell Biol. 11, 1-20).

Amino acid sequence identity among the DOR genes ranges from approximately 10-75%, with many genes showing a relatively low level of identity to each other (approximately 20%). Two pairs of clustered genes, 22A.1/22A.2 and 33B.1/33B.2 show the highest identity, with 75% and 57% homology, respectively. However, not all clustered genes show high degrees of similarity. 33B.3, for example, is only 28% identical to both 33B.1 and 33B.2 and 46F.1 and 46F.2 are only 29% identical. In addition to exhibiting sequence identity, many of the genes contain introns in corresponding locations (Figure 3), consistent with their constituting a family derived from a common ancestral gene. Examples of genomic DNA encoding the complete structural gene for DOR proteins containing the introns can be found in SEQ ID NO: 99-114, while the corresponding cDNA containing the intact ORF can be found in SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29 and 31.

There are sixty-seven residues that are conserved among at least 50% of the genes, and most of these (49) are in the C-terminal halves of the proteins (Figure 3). Among the conserved residues are a serine and a threonine in the intracellular C-terminal tail, residues frequently conserved in this region of GPCRs (Probst et al., (1992) DNA Cell Biol. 11, 1-20). The most divergent region in the sequences is a stretch of thirty amino acids representing part of the first extracellular loop and nearly all of transmembrane domain three. The divergence in this region also occurs in the most conserved pairs of genes: 22A.1 and 22A.2 are 75% identical overall, but only 50% identical in this region, and 33B.1 and 33B.2 are 57% identical overall, but only 33% identical in this region. This divergence has also been observed in other species. In particular, transmembrane domains three, four and five were exceptionally divergent in rat odorant receptors and have been proposed to play a role in odorant binding (Buck & Axel, (1991) Cell 65, 175-187).

Some of the genes are clustered in the genome (Figure 2A), while others are apparently isolated. Within a cluster the average intergenic distance is on the order of 500

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bases. Clustered DOR genes do not necessarily have introns in corresponding locations (e.g. 46F.1 and 46F.2), but all clustered genes have their transcriptional orientations in the same direction (Figure 2A). At least one of the DOR genes (2F.1) is flanked closely on both sides by two apparently unrelated genes (Figure 2B) (Haenlin et al., (1987) EMBO J. 6, 801-807).

A novel strategy to search the *Drosophila* genomic sequence database for genes encoding potential GPCRs was employed, leading to the identification of a multigene family with properties expected of odorant receptors. In addition to these genes, a wide variety of other transmembrane proteins were identified by this strategy, a few previously identified by other means and many representing novel proteins with similarity to known transmembrane proteins. These results suggest that the algorithm may be of widespread use in identifying new receptors, channels, and other transmembrane proteins.

The family of candidate odorant receptor genes currently contains forty-nine members, identified from the 16% of the *Drosophila* genomic sequence that is available. By extrapolation the size of this family may be on the order of 100 genes, making it the largest gene family identified in *Drosophila*.

There are several lines of evidence indicating that these genes encode *Drosophila* odorant receptors. First, the predicted proteins encoded by the genes each contain approximately seven potential transmembrane domains, as expected of GPCRs. Second, genes are expressed in one or both of the two olfactory organs, and for a number of genes this expression is restricted to a subset of olfactory receptors, as expected for odorant receptors. Third, the large number of family members, and the clustered location of many of these genes in the *Drosophila* genome, is reminiscent of odorant receptors in other organisms.

Additional lines of evidence is available which indicates DOR proteins as odor receptors. First, antibodies raised against the product of the DOR22A.2 gene label a small number of sensilla on the fly's antenna whose location corresponds to the same region labeled by in situ hybridization. Most important, staining appears localized to the cavities of the labeled sensilla, where the dendritic cells are located. This is exactly the localization expected of an odorant receptor. Second, different DOR genes are expressed (as determined by in situ

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hybridization) in different subsets of olfactory receptor neurons, as expected of odor receptor genes. Third, as expected, the number of olfactory receptor neurons labeled by individual DOR genes corresponds with the number of olfactory receptor neurons exhibiting a particular odor-sensitivity because the number of neurons expressing a particular DOR gene is predicted to equal the number of neurons with a particular odor response spectrum. Finally, many of the DOR genes are not expressed in the Acj6 POU-domain transcription factor mutant, where a subset of olfactory receptor neurons displayed abnormal odorant specificities. A correlation between DOR gene expression and odorant-specificity therefore exists, as is expected with odorant receptor genes.

Comparison of the sequences of these candidate odorant receptors to those from other organisms shows that they are extremely divergent from known odorant receptors and other GPCR families. This is not surprising, as searches for these genes based on sequence similarity to odorant receptors from other organisms had not succeeded, and the odorant receptor families in vertebrates and *C. elegans* are essentially unrelated. There is a great deal of sequence divergence among the DOR genes, much more than among the rat sequences previously reported (Buck & Axel, (1991) Cell 65, 175-187), for example. Moreover, genomic Southern blots have shown that none of nine DOR genes tested defines a subfamily of more than two or so well-conserved genes. The DOR family therefore differs in this respect from the mouse family, for example, where most odorant receptor genes belong to subfamilies of approximately seven to ten genes (Ressler *et al.*, (1993) Cell 73, 597-609).

Although at present the clusters of DOR genes identified thus far contain smaller numbers of genes (less than three) than in other organisms (Troemel *et al.*, (1995) Cell 83, 207-218; Sullivan *et al.*, (1996) Proc. Natl. Acad. Sci. USA 93, 884-888; Barth *et al.*, (1997) Neuron 19, 359-369), a number of interesting features of the clustered genes are already apparent. As found in other organisms (Barth *et al.*, (1997) Neuron 19, 359-369), *Drosophila* odorant receptor genes within a cluster are not necessarily coordinately regulated, such that genes within a cluster are expressed in different classes of cells, and even in different olfactory organs (*e.g.*, 46F.1 is expressed in the

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antenna). So far, all genes identified within a cluster, however, are transcribed in the same orientation. Genes within a cluster sometimes do, but sometimes do not, share intron positions, suggesting that introns may have become lost following gene duplication; a phylogenetic study revealed extensive gene duplication and intron loss among the chemoreceptor genes of *C. elegans* (Robertson, (1998) Genome Res. 8, 449-463).

Step 3: Identification of olfactory receptor genes using RT-PCR. RT-PCR with primers designed from two of these final candidates yielded amplification products from antennal cDNA. From RT-PCR experiments, the two genes did not appear to be expressed in the maxillary palp, abdomen, thorax, or head from which olfactory organs had been removed, suggesting that these genes were expressed specifically in the antenna. These two genes are located within 500 base pairs of each other at cytological position 22A (Figure 2A), and their predicted proteins are 75% homologous at the amino acid level.

For preparation of RNA, individual flies were frozen in liquid nitrogen, and antennae and maxillary palps were dissected. On average 150 antennae or 200 maxillary palps were used for RNA preparation. Total RNA was prepared as described elsewhere (McKenna et al., (1994) J. Biol. Chem. 269, 16340-16347). The RNA was treated with DNasel (Gibco-BRL) for thirty minutes at 37°C, phenol/chloroform extracted, and precipitated. The entire RNA preparation was used for oligo dT-primed cDNA synthesis using Superscript II Reverse Transcriptase (Gibco-BRL) according to the manufacturer's directions. PCR was performed using Taq polymerase (Sigma) under standard cycling conditions, with an annealing temperature of 60°C, gene-specific primer concentration of 1 pM, and magnesium concentration of 2.5 mM. For all genes except 2F.1, primer pairs which span introns were used in order to distinguish PCR bands amplified from cDNA from those amplified from any remaining genomic DNA.

Example 2: Hybridization of DOR gene probes to related sequences

To determine whether any of the DOR genes have closely related homologs, coding regions from nine of the genes were used to probe Southern blots of *Drosophila* genomic

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DNA at high or low stringency. For the closely related genes such as 22A.1 and 22A.2, a combined probe was used. For genomic southern blots, hybridizations were at 65°C (high stringency) or 55°C (low stringency), in 7% SDS, 0.5 M sodium-phosphate buffer pH 7.2, 1 mM EDTA, pH 8.0.

Each probe detected only its own sequence at high stringency, while at low stringency most gene probes detected one or two novel bands (data not shown). As expected, because of the overall low level of similarity, none of these extra bands corresponded to any of the other known DOR genes. These data indicate that some of these genes have one or two closely related homologs, but that none belongs to a large subfamily of highly related genes.

Example 3: Localization of DOR gene expression

Olfactory receptor neurons of the adult fly are located in both the antenna and the maxillary palp. To ask whether any of the DOR genes are expressed in these neurons, in situ hybridization was carried out using adult tissue sections.

For *in situ* hybridization experiments, coding regions of the DOR genes were subcloned into the pGEM-T Easy vector (Promega). Digoxygenin-labeled RNA probes were generated and hydrolyzed according to the manufacturer's instructions (Boehringer Mannheim). *In situ* hybridizations to RNA in tissue sections were performed using a modified version of procedures described elsewhere (Roberts, (1998) *Drosophila*: A Practical Approach, Oxford University Press; Chadwick & McGinnis, (1987) EMBO J. 6, 779-789). Briefly, heads were dissected from animals and fixed in 4% paraformaldehyde/PBS for fifteen minutes. Tween-20 was then added to 0.1% and heads were fixed for an additional thirty minutes. Samples were washed twice for five minutes in 0.1% Tween 20/PBS (PBST), cut into 8 µm frozen sections, and mounted on poly-L-Lysine treated slides (Sigma). Sections were dried onto slides for thirty minutes at room temperature and then fixed for an additional thirty minutes in 4% paraformaldehyde/PBST. Samples were washed for a total of two hours in PBST with five changes of buffer, followed by an incubation for five minutes in 1:1 PBST:hybridization buffer (50% formamide, 5× SSC, 50 mg/ml heparin, 0.1% Tween 20),

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and then prehybridized for two hours at 55°C.

Of eleven genes examined, seven displayed detectable expression, which in every case was restricted to the olfactory organs (Table 2). The 46F.1 probe hybridized to a subset of olfactory receptors in the maxillary palp (Figure 4A). Counting of labeled olfactory receptors in serial sections revealed that the total number of 46F.1-staining olfactory receptors per maxillary palp was 18±1 (Table 2), or 15% of the 120 olfactory neurons in the maxillary palp. A similar number of neurons, 17±1, was labeled by another probe, 33B.3 (Figure 4B). The neuronal identity of the labeled cells was apparent from the presence in many cases of a well-defined axon projecting from the labeled cell body and joining the maxillary nerve (Figures 4B-C). For both probes, the labeled neurons were distributed broadly over the olfactory surface of the organ, and were interspersed among unlabeled neurons (Figures 4A-C). Staining in many cells appeared annular, which was interpreted to reflect a perinuclear distribution of mRNA, as expected of an mRNA present at highest concentrations in the cell bodies of these olfactory receptors (Figure 4B). The 33B.3 and 46F.1 genes are evidently expressed in different subsets of olfactory receptors, because the number of neurons hybridizing with a mixed probe was greater than the number of neurons that hybridized when either probe was used individually (data not shown). No hybridization detected in the antenna, head, or thorax for either probe.

Many of the DOR genes are expressed in the antenna and not in the maxillary palp, as determined by RT-PCR (Table 1). For several genes this localization was confirmed by *in situ* hybridization. The 47E.1 probe hybridized to 40±1 cells in a broad area across the antenna (Figures 5A-B), including both anterior and posterior faces, similar to the distribution pattern of small s. basiconica (Figure 1F). A probe from the 25A.1 gene hybridized to fewer cells, 16±1, but in a region of the antenna similar to that of 47E.1 staining, as judged by reconstruction of serial sections (Figure 5C-D). The 22A.2 probe hybridized to 22±1 cells in a different distribution, clustered in the dorso-medial region of the antenna (Figure 5E). This pattern matches the distribution of the large s. basiconica (Figure 1E). The expression patterns of the three genes in the antenna are illustrated schematically in Figure 5G. None of

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these three probes revealed expression in the maxillary palp, head, or thorax. This data demonstrates that the DOR family is expressed in olfactory receptors, and that the expression of individual members is restricted to distinct subsets of cells in the olfactory organs.

The number and broad distribution of maxillary palp neurons expressing 46F.1 and 33B.3 are intriguing in light of electrophysiological studies. There are approximately 120 olfactory receptors on the palp, which fall into six different classes based upon their odorant response profiles. Each class contains roughly equal numbers of neurons, distributed broadly over the olfactory surface of the palp. Thus, if an individual receptor gene is expressed in all olfactory receptors of a functional class, one might expect a gene to be expressed in a broad distribution, in approximately twenty neurons, in good agreement with the distribution and numbers observed for both 46F.1 and 33B.3 (18±1 and 17±1, respectively).

The two DOR genes whose expression was detected by in situ hybridization in the maxillary palp are expressed in olfactory receptors housed within s. basiconica, the only morphological class of sensilla on the palp. In the antenna, the 22A.2 probe consistently hybridized to a subset of cells in a portion of the dorso-medial region of the antenna that contains almost exclusively large s. basiconica (Figure 1E). The 47E.1 and 25A.1 probes hybridize to subsets of cells in a distinctly different region of the antenna which may correlate with the distribution of small s. basiconica, of which at least two functional types are intermingled (Figure 1F). Of particular interest, the numbers of cells to which 47E.1 and 25A.1 hybridize are different: 40±1 and 16±1; one possible interpretation is that they are expressed in distinct functional types of small s. basiconica. This region also contains s. trichodea and s. coeloconica, and although the labeling patterns do not correlate with the distribution of either of two functional classes of s. trichodea (Clyne et al., (1997) Invert. Neurosci. 3, 127-135), a definitive identification of the sensillar type may require further investigation. If in fact all the DOR genes are expressed in only one of the morphological categories of sensilla, the s. basiconica, it is possible that there are other, as yet unidentified, families of receptors that are expressed in the other morphological categories of sensilla. This would mean that the number of odorant receptors in Drosophila might be substantially larger

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than one-hundred.

Applicants have identified three DOR genes that are expressed in the maxillary palp (Table 1), from the 16% of the genome analyzed. As these three genes, like most DOR genes, are not clustered in the genome, linear extrapolation suggests that the entire genome contains on the order of eighteen DOR genes expressed in the maxillary palp, an organ which has six functional classes of neurons (Clyne et al., (1999) Neuron 22, 339-347; de Bruyne et al., (1999) J. Neurosci. 19, 4520-4532). If all neurons within a functional class, i.e. with the same odor-specificity, are identical in terms of their receptor expression, then the ratio of expressed genes to neuronal classes in this organ would be consistent with a model in which an individual ORN expresses a small number of odorant receptors; however, further data is needed to establish conclusively the number of receptor genes expressed per cell. Olfactory neurons in other organisms appear to lie at either of two extremes: in the vertebrates, it is believed only one receptor is expressed per ORN (Ngai et al., (1993) Cell 72, 667-680; Ressler et al., (1993) Cell 73, 597-609; Vassar et al., (1993) Cell 74, 309-318); in C. elegans, approximately 550 chemoreceptors are likely to be distributed amongst fourteen classes of chemosensory neurons (Troemel et al., (1995) Cell 83, 207-218).

Olfactory receptors in *Drosophila* and other insects project to an olfactory processing center, the antennal lobe, which is much like the olfactory bulb of vertebrates. Like its vertebrate counterpart, the antennal lobe contains olfactory glomeruli, of which the antennal lobe of *Drosophila* has approximately forty (Stocker *et al.*, (1995) Roux's Arch Dev Biol 205, 62-72; Laissue *et al.*, (1999) J. Comp. Neurol. 405, 543-552). In vertebrates there is an approximate equivalence between the estimated number of odorant receptor genes and the number of glomeruli (Barth *et al.*, (1996) Neuron 16, 23-34; Buck, (1996) Annu. Rev. Neurosci. 19, 517-544); since *C. elegans* does not contain glomeruli, it has not been possible until now to consider whether the evolutionary conservation of this equivalence extends to invertebrates. If in fact the number of DOR genes is one-hundred, then the ratio of odorant receptor genes to glomeruli would exceed two, and would rise if additional families of odorant receptor genes were discovered. Of particular interest, the number of glomeruli receiving

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input from the maxillary palp has been variously estimated as three and five (Venkatesh & Singh, (1984) Int. J. Insect. Morphol. Embryol. 13, 51-63; Stocker *et al.*, (1995) Roux's Arch Dev Biol 205, 62-72); if our estimate of eighteen genes expressed in the maxillary palp is correct, then the ratio of these receptor genes to their corresponding glomeruli would fall in the range of three to six.

Example 4: DOR gene expression during development

Recent evidence supports a dual role for the vertebrate olfactory receptors. First, these receptors have an instructive role in guiding the axons of olfactory receptors to the correct glomeruli during development (Mombaerts et al., (1996) Cell 87, 675-686; Wang et al., (1998) Cell 93, 47-60), and second as odorant receptors in the adult (Zhao et al., (1998) Science 279, 237-242). To address the possibility that the DOR genes might also play a role in development, three DOR probes were hybridized to antennal sections from different stages of pupal development. In Drosophila, ORN axons first leave the developing antenna at approximately sixteen hours after puparium formation (APF) (Lienhard & Stocker, (1991) Development 112, 1063-1075; Ray & Rodrigues, (1995) Dev. Biol. 167, 426-438; Reddy et al., (1997) Development 124, 703-712), and the diameter of the antennal nerve continues to increase until 72 hours APF (Stocker et al., (1995) Roux's Arch. Dev. Biol. 205, 62-72). Glomeruli first become visible in the antennal lobe at approximately 48 hours APF. Developing antennae were therefore examined at 16, 24, 36, 48, 54, 60, 72 and 93 hours APF (adults eclosed from the pupal case at approximately 100 hours). For these developmental studies, Drosophila were collected as white prepupae and kept at 25°C on moist filter paper for the indicated number of hours, at which time they were fixed. At 25°C the approximate time from the white prepupal stage to eclosion is 100 hours (Lockett & Ashburner, (1989) Dev. Biol. 134, 430-437).

Cells positive for 22A.2 were first seen at 60 hours APF, indicating that detectable expression begins between 54 and 60 hours, well within the period in which the antennal nerve is still increasing in diameter (Figure 6A-B). A subset of cells was labeled at this time,

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and they were restricted to a subregion of the developing antenna; the pattern appears comparable to that of the mature antenna, although this pattern was not characterized in as much detail as that of the adult. Labeling with 22A.2 was also observed in antennae at all subsequent time points. Interestingly, cells positive for 47E.1 and 25A.1 were not observed until much later, at the 93 hour time point; they were not observed at any of the earlier times (Figure 6C-D and data not shown). For comparison, *in situ* hybridization was also performed with a probe representing the odorant-binding protein OS-E (McKenna *et al.*, (1994) J. Biol. Chem. 269, 16340-16347), which is believed to play a role in olfactory function, but which has not been implicated in a developmental process. OS-E was also first observed at 93 hours, at which time it expression increased (Figure 6E-F).

Example 5: Regulation of DOR expression by POU domain transcription factor acj6

Little is known about the regulation of odor receptor genes, a process critical to the establishment of olfactory neuron identity and ultimately to the process of olfactory coding. In *C. elegans* the *odr7* gene, a member of the nuclear receptor superfamily, has been shown to regulate the odorant receptor gene *odr10* (Sengupta *et al.*, (1994) Cell 79, 971-980; Sengupta *et al.*, (1996) Cell 84, 899-909). In *Drosophila*, null mutations of the *acj6* gene, which encodes a POU domain transcription factor, eliminate the odor response of three of the six classes of maxillary palp olfactory receptors (Clyne *et al.*, (1999) Neuron 22, 339-347). A fourth ORN class on the maxillary palp is altered to a new class of ORN with a novel odor sensitivity. These data suggest that Acj6 plays a role in the differentiation of certain maxillary palp olfactory receptors, perhaps by determining which olfactory receptor gene(s) are expressed. To address the possibility that Acj6 regulates odorant receptor genes, probes from the 33B.3 and 46F.1 genes were hybridized to sections of maxillary palps from the null mutant, *acj6*⁶. No hybridization was detected in either case (Figure 4D and data not shown), nor was expression of either gene detected by RT-PCR from *acj6*⁶ maxillary palps (Table 1).

acjó mutations also affect the physiological response of the antennal neurons to odors (Ayer & Carlson, (1991) Proc. Nat. Acad. Sci. USA 88, 5467-5471; Ayer & Carlson, (1992)

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J. Neurobiol. 23, 965-982). 22A.2, 25A.1, and 47E.1 probes were therefore hybridized to sections of $acj6^6$ antennae. All three probes hybridized to groups of cells in the same locations as in the wild type antenna (Figure 5F and data not shown). RT-PCR amplification showed that expression of certain other DOR genes, 33B.1, 33B.2, 33B.3, and 46F.2 was eliminated in the antenna of $acj6^6$ (Table 1). Thus, in the $acj6^6$ mutant, one subset of candidate odorant receptor genes was not expressed while a different subset remained unaffected. Interestingly, genes within a cluster all showed similar dependency on Acj6: 33B.1, 33B.2, and 33B.3, for example, all depended on Acj6, whereas 22A.1 and 22A.2 did not. In summary, these data support a role for acj6 in the regulation of a subset of olfactory receptor genes.

The DOR family is subject to complex regulation. First, the expression of individual DOR genes exhibits highly specific tissue and spatial localization. Some genes are expressed in the antenna but not the maxillary palp; others show expression in the maxillary palp but not the antenna. Within an organ, expression of a particular DOR gene is restricted to a subset of cells. In the antenna, the patterns of expression are spatially regulated, exhibiting regional specificity of expression as detailed above. In the maxillary palp, expression is limited to a population of neurons approximately equal in number to the neurons of a functional class.

DOR genes are also subject to interesting temporal regulation. One gene, 22A.2, is expressed in the developing antenna during a time when the antennal nerve is still increasing in diameter (Stocker et al., (1995) Roux's Arch. Dev. Biol. 205, 62-72). These data leave open a possible role for *Drosophila* olfactory receptors in axon guidance and glomerulus formation, a role for which evidence has been found in vertebrates (Mombaerts et al., (1996) Cell 87, 675-686; Wang et al., (1998) Cell 93, 47-60) but not *C. elegans*. In zebrafish, odorant receptors show asynchronous onset of expression during development of the olfactory placode (Barth et al., (1996) Neuron 16, 23-34). The DOR genes also show heterogeneity in their temporal regulation: expression of two other DOR genes begins much later than for the 22A.2 gene. If in fact individual olfactory receptors express more than one DOR gene, perhaps some have acquired a specialized role in development.

Evidence also exists indicating that different DOR genes are expressed at different

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levels of abundance within cells. Although RT-PCR experiments demonstrated expression of 25A.1 in both antenna and maxillary palp, in situ hybridization revealed expression of 25A.1 only in the antenna of each animal examined; conversely, although RT-PCR experiments showed expression of 33B.3 in both olfactory organs, in situ hybridization detected label only in the maxillary palp of each animal examined (Tables 1 and 2). These results suggest that a receptor gene may be expressed at different cellular levels in the two organs, and that different genes may be expressed at different cellular levels in the same organ. Such an explanation would suggest that there are mechanisms governing not only the spatial and temporal control of DOR genes, but also their levels of expression.

If DOR genes are in fact expressed at different cellular levels in particular olfactory receptors, then perhaps the four DOR genes that were undetectable in the antenna by *in situ* hybridization, despite clear evidence for their antennal expression from RT-PCR, a more sensitive technique, are among those expressed at low levels. It is important to note that in *C. elegans*, expression of a number of candidate odorant receptors was undetectable using GFP fusion genes (Troemel *et al.*, (1995) Cell 83, 207-218).

As a first step in investigating the mechanisms through which the complex regulation of DOR genes is achieved, the role of the POU domain transcription factor Acj6 was tested, which was previously found to act in governing olfactory neuron identity. Applicants found that Acj6 is in fact required for expression of the DOR family. Two lines of evidence, RT-PCR and *in situ* hybridization analysis, both indicate that proper expression of a specific subset of DOR genes depends on Acj6. The results indicate that the odor-specificity of a subset of olfactory receptors is governed at least in part by the action of the Acj6 POU domain transcription factor on DOR genes, and are fully consistent with the notion that DOR genes encode odorant receptors.

The isolation of genes likely to encode odorant receptors in *Drosophila* opens a number of avenues for future investigation. Drosophila provides the ability to manipulate odor receptors genetically and test the functional consequences of such manipulations in vivo, either physiologically or behaviorally. Such analysis may be useful in examining potential

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roles of DOR proteins in olfactory response and in development. It may also be possible to isolate homologous genes in other insects, including some which provide excellent opportunities for research and some of agricultural or medical importance which rely on olfactory cues to locate their hosts.

Example 6: Transgenic Drosophila

P element mediated germline transformation of Drosophila can be carried out as previously described (Rubin & Spradling, (1982) Science 218, 348-353). *Drosophila* embryos are isolated and microinjected with P element expression constructs as previously described (Karess & Rubin, (1984) Cell 38, 135-146) containing a particular DOR nucleotide sequence, at 0.5 mg/ml together with a helper plasmid at 0.1 mg/ml. Go injected adults are individually back crossed to the recipient strain and the Go progeny screened for the w+transformation marker (Klemenz *et al.*, (1987) Nucleic Acids Res. 10, 3947-3959).

Transformed lines homozygous for the transgene are established from orange eyed Go flies as previously described (Klemenz *et al.*, (1987) Nucleic Acids Res. 10, 3947-3959).

A line of *Drosophila* in which the DOR33B.3 gene can be over-expressed was constructed as described above. The DOR33B.3 coding sequences were joined to an upstream activating sequence (UAS) and introduced by P element-mediated germline transformation into *Drosophila*. A yeast GAL4 transcription factor gene, coupled to a heat shock promoter, was then crossed into the transgenic line. As expected, heat shock of this line resulted in induction of DOR33B.3 expression. The heat shock-induced expression of GAL4, results in binding of GAL4 to the UAS, and subsequent induction of DOR33B.3 expression. This transgenic line of *Drosophila*, and three other transgenic lines containing other DOR genes, can be tested for elevated responses to any of fifty different odors. Elevated response to any particular odorant is indicative of an ligand which binds and activates the over-expressed receptor (see, e.g., Zhao & Firestein, (1998) Science 279, 237-242).

Although the present invention has been described in detail with reference to

examples above, it is understood that various modifications can be made without departing from the spirit of the invention. Accordingly, the invention is limited only by the following claims. All cited patents and publications referred to in this application are herein incorporated by reference in their entirety. The results of the experiments disclosed herein have been published in the journal Neuron (22, 327-338) in February, 1999, this article herein incorporated by reference in its entirety.

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We claim:

- 1. An isolated nucleic acid molecule selected from the group consisting of:
- a) an isolated nucleic acid molecule that encodes the amino acid sequence of a *Drosophila* Odorant Receptor protein;
- b) an isolated nucleic acid molecule that encodes a protein fragment of at least 6 amino acids of a *Drosophila* Odorant Receptor protein; and
- c) an isolated nucleic acid molecule which hybridizes to a nucleic acid molecule comprising a nucleotide sequence encoding a *Drosophila* Odorant Receptor protein under conditions of sufficient stringency to produce a clear signal.
- 2. The isolated nucleic acid molecule of claim 1 wherein the nucleic acid comprises at least one exon-intron boundary located in a position selected from the group consisting of:
- a) the nucleotides encoding the amino acids which comprise the third extracellular domain of a Drosophila Odorant Receptor protein;
- b) the nucleotides encoding the amino acids which comprise the fourth extracellular domain of a *Drosophila* Odorant Receptor protein; and
- c) the nucleotides encoding the amino acids which comprise the fourth intracellular domain of a *Drosophila* Odorant Receptor protein.
- 3. The isolated nucleic acid molecule of claim 1, wherein the nucleic acid molecule is selected from the group consisting of SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95 and 97.
- 4. The isolated nucleic acid molecule of any one of claims 1-3, wherein said nucleic acid molecule is operably linked to one or more expression control elements.

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- 5. A vector comprising an isolated nucleic acid molecule of any one of claims 1-3.
- A host cell transformed to contain the nucleic acid molecule of any one of claims 1-3.
 - 7. A host cell comprising a vector of claim 5.
- A host cell of claim 7, wherein said host is selected from the group consisting of prokaryotic hosts and eukaryotic hosts.
- 9. A method for producing a protein or protein fragment comprising the step of culturing a host cell transformed with the nucleic acid molecule of any one of claims 1-3 under conditions in which the protein or protein fragment encoded by said nucleic acid molecule is expressed.
- 10. The method of claim 9, wherein said host cell is selected from the group consisting of prokaryotic hosts and eukaryotic hosts.
 - 11. An isolated protein or protein fragment produced by the method of claim 10.
 - 12. An isolated protein or protein fragment selected from the group consisting of:
 a) an isolated protein comprising one of the amino acid sequences depicted in SEQ ID
 NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50,
 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96 and 98;
- b) an isolated protein fragment comprising at least 6 amino acids of any of the sequences depicted in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96 and 98;

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- c) an isolated protein comprising conservative amino acid substitutions of any of the sequences depicted in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96 and 98; and
- d) naturally occurring amino acid sequence variants of any of the sequences depicted in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96 and 98.
- 13. The isolated protein or protein fragment of claim 12 wherein the protein or protein fragment has at least one of the following conserved amino acids selected from the group consisting of:
 - a) Leucine in the third extracellular domain of a Drosophila Odorant Receptor protein;
- b) Histidine in the third extracellular domain of a *Drosophila* Odorant Receptor protein;
 - c) Cysteine in the sixth transmembrane domain of a ${\it Drosophila}$ Odorant Receptor protein;
 - d) Tryptophan in the fourth extracellular domain of a *Drosophila* Odorant Receptor protein;
- e) Glutamine in the seventh transmembrane domain of a *Drosophila* Odorant Receptor protein;
- f) Proline in the seventh transmembrane domain of a Drosophila Odorant Receptor protein;
- g) Alanine in the fourth intracellular domain of a $\ensuremath{\textit{Drosophila}}$ Odorant Receptor protein; and
- h) Tyrosine in the fourth intracellular domain of a ${\it Drosophila}$ Odorant Receptor protein.

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- 14. An isolated antibody that binds to a polypeptide of claim 11, 12 or 13.
- The antibody of claim 14 wherein said antibody is a monoclonal or polyclonal antibody.
- 16. A method of identifying an agent which modulates the expression of a protein or protein fragment of claim 11, 12 or 13 comprising the steps of:
 - a) exposing cells which express the protein or protein fragment to the agent; and
- b) determining whether the agent modulates expression of said protein or protein fragment, thereby identifying an agent which modulates the expression of a protein or protein fragment of claim 11, 12 or 13.
- 17. A method of identifying an agent which modulates the activity of a protein or protein fragment of claim 11, 12 or 13 comprising the steps of:
 - a) exposing cells which express the protein or protein fragment to the agent; and
- b) determining whether the agent modulates the activity of said protein or protein fragment, thereby identifying an agent which modulates the activity of a protein or protein fragment of claim 11, 12 or 13.
- 18. The method of claim 17, wherein the agent modulates at least one activity of the protein or protein fragment.
- 19. A method of identifying an agent which modulates the transcription of the nucleic acid molecule of any one of claims 1-3 comprising the steps of:
 - a) exposing cells which transcribe the nucleic acid to the agent; and
- b) determining whether the agent modulates transcription of said nucleic acid, thereby identifying an agent which modulates the transcription of the nucleic acid molecule of any one of claims 1-3.

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- 20. A method of identifying binding partners for a protein or protein fragment of either claim 11, 12 or 13 comprising the steps of:
 - a) exposing said protein or protein fragment to a potential binding partner; and
- b) determining if the potential binding partner binds to said protein or protein
 fragment, thereby identifying binding partners for the protein or protein fragment.
 - 21. A method of modulating the expression of a nucleic acid encoding a protein or protein fragment of claim 11, 12 or 13 comprising administering an effective amount of an agent which modulates the expression of a nucleic acid encoding the protein or protein fragment.
 - 22. A method of modulating at least one activity of a protein or protein fragment of claim 11, 12 or 13 comprising the step of administering an effective amount of an agent which modulates at least one activity of the protein or protein fragment.
 - 23. A method of identifying novel olfactory receptor genes comprising the steps of:
 - a) selecting candidate olfactory receptor genes by screening a nucleic acid database using an algorithm trained to identify seven transmembrane receptors genes;
 - b) screening said selected candidate olfactory receptor genes by identifying nucleic acid sequences with conserved amino acid residues and intron-exon boundaries common to olfactory receptors, and having open reading frames of sufficient size so as to encode a seven transmembrane receptor; and
 - c) identifying the novel olfactory receptor genes and measuring the expression of olfactory receptor genes wherein the detection of expression confirms said candidate olfactory gene as an olfactory gene.
 - 24. A method of identifying novel olfactory receptor genes comprising the steps of:
 - a) selecting candidate olfactory receptor genes by screening a nucleic acid database for

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nucleic acid sequences with sufficient homology to at least one known olfactory receptor gene;

- b) screening said selected candidate olfactory receptor genes by identifying nucleic acids with conserved amino acid residues and intron-exon boundaries common to olfactory receptors, and having open reading frames of sufficient size so as to encode a seven transmembrane receptor; and
- c) identifying the novel olfactory receptor genes and measuring the expression of olfactory receptor genes wherein the detection of expression confirms said candidate olfactory gene as an olfactory gene.
- A transgenic insect modified to contain a nucleic acid molecule of any of claims
 1-3.
- 26. The transgenic insect of claim 25, wherein the nucleic acid molecule contains a mutation that alters expression of the encoded protein.

ABSTRACT

The present invention provides nucleic acids and amino acids for novel olfactory receptors as well as methods for identifying olfactory receptors. More specifically, the present invention provides nucleic acids and amino acids for novel olfactory receptors in Drosophila as well as methods of using the provided nucleic acids and amino acids. In addition, this invention provides methods of identifying ligands which bind to the novel olfactory receptors as well as a variety of methods for using the ligands so identified.

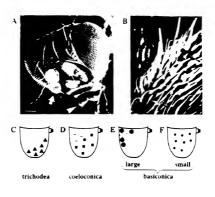


Figure 1

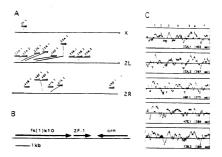


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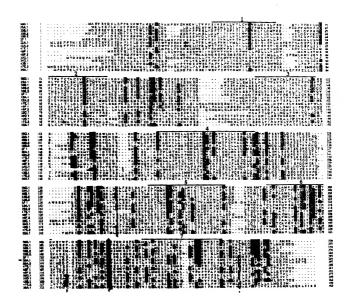


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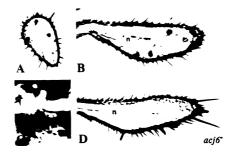


Figure 4

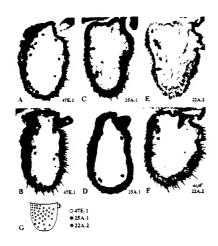


Figure 5

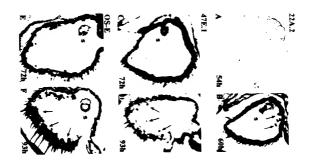


Figure 6

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:)	e =
John R. Carlson et al.)	a Lis
Application No.:) Group Art Unit:	9/49
Filed: January 25, 2000) Examiner:	jc5.
For: NOVEL FAMILY OF ODORANT RECEPTORS IN DROSOPHILA	.)	

Assistant Commissioner for Patents Washington, D.C. 20231

BOX SEQUENCE

STATEMENT ACCOMPANYING SEQUENCE LISTING

Dear Sir:

The undersigned hereby states upon information and belief that the Sequence Listing submitted concurrently herewith does not include matter which goes beyond the content of the application as filed and that the information recorded on the diskette submitted concurrently herewith is identical to the written Sequence Listing submitted herewith.

Respectfully submitted,

MORGAN, LEWIS & BOCKIUS LLP

Dated: January 25, 2000 By: Young Wossen
Printed Name: Rosanne Kosson

MORGAN, LEWIS & BOCKIUS LLP 1800 M Street, N.W. Washington, D.C. 20036 (202) 467-7000

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tcc ttt ggc tgg aca gtg cct gaa aac aaa agg tgg gat cta cat tac
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Lys Leu Trp Ser Thr Phe Val Thr Leu Leu Ile Phe Ile Leu Leu Pro $50 \ \ 55 \ \ 60$

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Gly Glu Phe Leu Ser Ser Ile Gln Ile Gly Val Asn Met Tyr Gly Ser 85 90 95

Ser Phe Lys Ser Tyr Leu Thr Met Met Gly Tyr Lys Lys Arg Gln Glu 100 105 110

Ala Lys Met Ser Leu Asp Glu Leu Asp Lys Arg Cys Val Cys Asp Glu 115 120 125

Glu Arg Thr Ile Val His Arg His Val Ala Leu Gly Asn Phe Cys Tyr 130 135 140

Ile Phe Tyr His Ile Ala Tyr Thr Ser Phe Leu Ile Ser Asn Phe Leu 145 150 150 160

Ser Phe Ile Met Lys Arg Ile His Ala Trp Arg Met Tyr Phe Pro Tyr \$165\$ \$170\$

Leu Arg Gly Trp Ala Val Phe Met Asp Leu Cys Thr Asp Val Cys Pro \$195\$

Leu Ile Ser Met Val Ile Ala Arg Cys His Ile Thr Leu Leu Lys Gln

Leu Lys Glu Leu Ala Asp Cys Val Arg Asp His Arg Leu Ile Leu \$245\$ \$250\$ \$250

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Pro Arg Ile Ser Gly Leu Ile Val Gly Leu Trp Pro Gln Arg Ile Arg
20 25 30

ggc ggg ggt cgt cct tgg cac gcc cat ctg ctc ttc gtg ttc gcc $\,$ 144 Gly Gly Gly Arg Pro Trp His Ala His Leu Leu Phe Val Phe Ala $\,$ 45 $\,$

tte gee atg gtg gtg ggt ggt ggt ggt ggt ggt gtg teg tae ggc tgt $$\,^{192}$ Phe Ala Met Val Val Gly Ala Val Gly Glu Val Ser Tyr Gly Cys 50

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acc acc aag gcg gtc tgc gtt ttg aag ctg tgg gtc ttc ttc egc tcc \$288\$ Thr Thr Lys Ala Val Cys Val Leu Lys Leu Trp Val Phe Phe Arg Ser \$85\$

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												gtg Val				432
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gcc Ala	tgc Cys	acc Thr	gtt Val 180	ttc Phe	gcc Ala	ttc Phe	agc Ser	ttc Phe 185	gtg Val	gac Asp	gga Gly	ttc Phe	ttc Phe 190	att Ile	tgc Cys	576
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ato Ile	tgo Cys	tat	ato	ato	gcç Ala	gcc Ala	cta Leu	aco Thi	caç Glr	cta Leu	a tto 1 Phe	ctc Leu	tac Tyr	tgc Cys	ttc Phe	912

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Asr	n Arç	g Ar	g Trp	Ala	Glı	ı Lev	ı Val	Glr	n Arg	Let	a Arç	, Ala	Ile	e Leu	Leu	

100 105 110

Ser Leu Leu Leu Ser Ser Gly Thr Ala Thr Asn Ala Ala Phe Thr

Leu Gln Pro Leu Ile Met Gly Leu Tyr Arg Trp Ile Val Gln Leu Pro 130 135 140

Gly Gln Thr Glu Leu Pro Phe Asn Ile Ile Leu Pro Ser Phe Ala Val 145 150 155 160

Gln Pro Gly Val Phe Pro Leu Thr Tyr Val Leu Leu Thr Ala Ser Gly $$^{\circ}$$ 165 \$170\$ 170 \$175\$

Ala Cys Thr Val Phe Ala Phe Ser Phe Val Asp Gly Phe Phe Ile Cys $180 \,$ $185 \,$ $190 \,$

Ser Cys Leu Tyr Ile Cys Gly Ala Phe Arg Leu Val Gln Gln Asp Ile 195 200 205

Arg Arg Ile Phe Ala Asp Leu His Gly Val Asp Val Phe Thr Glu Glu 210 215 220

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Ile Leu Asp Ile Met Leu Asn Thr Ser Ser Leu Ser Gly Leu Thr Tyr

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Gly Gly Asn His Val Ser Glu Ser Ser Ala Ala Val Ala Asp Val Leu 305 310 315 320

Tyr Asp Met Glu Trp Tyr Lys Cys Asp Ala Arg Thr Arg Lys Val Ile 325 330 335

Leu Met Ile Leu Arg Arg Ser Gln Arg Ala Lys Thr Ile Ala Val Pro \$340\$ \$350\$

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DOWSTRY OFFICE

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Val	. Asp	Glr	n Ser	325		Туг	Arg	Gly	His 330	Met	. Leu	Ile	. Leu	335	Glu
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Ser	Ser	Ile	Leu	Ser	Leu	Val	Lys	Met	Val	Ala	Ile	Trp	Trp	Tyr	Gln	
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Gln	Leu	Thr	Phe	Leu	Leu	Leu	Cys	Cys	Gly	Phe	Cys	Thr	Ser	Thr	Ser	
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135

Tyr Ser Val Arg His Leu Ile Asp Asn Ile Leu Arg Arg Thr His Gly

Lys Asp Trp Ile Tyr Glu Thr Pro Phe Lys Met Met Phe Pro Asp Leu 145 150 155 160

Leu Leu Arg Leu Pro Leu Tyr Pro Ile Thr Tyr Ile Leu Val His Trp \$165\$ \$170\$ \$175\$

His Gly Tyr Ile Thr Val Val Cys Phe Val Gly Ala Asp Gly Phe Phe 180 185 190

Leu Gly Phe Cys Leu Tyr Phe Thr Val Leu Leu Leu Cys Leu Gln Asp \$195\$

Asp Val Cys Asp Leu Leu Glu Val Glu Asn Ile Glu Lys Ser Pro Ser 210 215 220

Glu Ala Glu Glu Ala Arg Ile Val Arg Glu Met Glu Lys Leu Val Asp 225 230 235

Arg His Asn Glu Val Ala Glu Leu Thr Glu Arg Leu Ser Gly Val Met \$245\$

Val Glu Ile Thr Leu Ala His Phe Val Thr Ser Ser Leu Ile Gly $260 \\ 265 \\ 270 \\$

Thr Ser Val Val Asp Ile Leu Leu Phe Ser Gly Leu Gly Ile Ile Val \$275\$

Tyr Val Val Tyr Thr Cys Ala Val Gly Val Glu Ile Phe Leu Tyr Cys 290 \$295\$ 300

Leu Gly Gly Ser His Ile Met Glu Ala Cys Ser Asn Leu Ala Arg Ser 305 310 315 320

Thr Phe Ser Ser His Trp Tyr Gly His Ser Val Arg Val Gln Lys Met \$325\$ \$330\$ \$335

Thr Leu Leu Met Val Ala Arg Ala Gln Arg Val Leu Thr Ile Lys Ile 340 345 350

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DOMOTEZ, OTARCO

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_	cta Leu			_	-	-										816
	gcc Ala															864
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	gtt Val	_		-		_	_									960
	gcc Ala															1008
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Pro 65	Ile	Asn	Tyr	Val	Ile 70	His	Leu	Ala	Glu	Phe 75	Pro	Pro	Glu	Leu	Leu 80	
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Phe	Phe	Thr	Leu 100	Ile	Val	Tyr	Thr	His 105	Arg	Leu	Glu	Leu	Ala 110	Asn	Lys	
His	Phe	Asp	Glu	Leu	Asp	Lys	Tyr 120	Cys	Val	Lys	Pro	Ala 125	Glu	Lys	Arg	

- Lys Val Arg Asp Met Val Ala Thr Ile Thr Arg Leu Tyr Leu Thr Phe $130\,$
- Val Val Val Tyr Val Leu Tyr Ala Thr Ser Thr Leu Leu Asp Gly Leu 145 155 160
- Leu His His Arg Val Pro Tyr Asn Thr Tyr Tyr Pro Phe Ile Asn Trp \$165\$
- Arg Val Asp Arg Thr Gln Met Tyr Ile Gln Ser Phe Leu Glu Tyr Phe \$180\$ \$190\$
- Thr Val Gly Tyr Ala Ile Tyr Val Ala Thr Ala Thr Asp Ser Tyr Pro \$195\$ 200 205
- Val Ile Tyr Val Ala Ala Leu Arg Thr His Ile Leu Leu Leu Lys Asp $210 \ \ 215 \ \ \ 220 \ \ \$
- Arg Ile Ile Tyr Leu Gly Asp Pro Ser Asn Glu Gly Ser Ser Asp Pro 225 230 235 240
- Ser Tyr Met Phe Lys Ser Leu Val Asp Cys Ile Lys Ala His Arg Thr \$245\$ \$250\$
- Met Leu Asn Phe Cys Asp Ala Ile Gln Pro Ile Ile Ser Gly Thr Ile 260 \$265\$
- Phe Ala Gln Phe Ile Ile Cys Gly Ser Ile Leu Gly Ile Ile Met Ile \$275\$ \$280\$ \$285\$
- Asn Met Val Leu Phe Ala Asp Gln Ser Thr Arg Phe Gly Ile Val Ile 290 295 300
- Tyr Val Met Ala Val Leu Leu Gln Thr Phe Pro Leu Cys Phe Tyr Cys 305 \$310\$ \$315 \$320
- Asn Ala Ile Val Asp Asp Cys Lys Glu Leu Ala His Ala Leu Phe His 325 \$330\$
- Ser Ala Trp Trp Val Gln Asp Lys Arg Tyr Gln Arg Thr Val Ile Gln \$340\$ \$345\$ \$350\$
- Phe Leu Gln Lys Leu Gln Gln Pro Met Thr Phe Thr Ala Met Asn Ile 355 360 365

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Trp Leu Tyr Trp Arg Leu Leu Gly Val Glu Gly Asp Tyr Pro Phe Arg
             20
                                                      30
cgg cta gtg gat ttt aca atc acg tct ttc att acg att tta ttt ccc
                                                                   144
Arg Leu Val Asp Phe Thr Ile Thr Ser Phe Ile Thr Ile Leu Phe Pro
         35
                             40
gtg cat ctt ata ctg gga atg tat aaa aag ccc cag att caa gtc ttc
                                                                   192
Val His Leu Ile Leu Gly Met Tyr Lys Lys Pro Gln Ile Gln Val Phe
     50
                         55
agg agt ctg cat ttc aca tcg gaa tgc ctt ttc tgc agc tat aag ttt
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Arg Ser Leu His Phe Thr Ser Glu Cys Leu Phe Cys Ser Tyr Lys Phe
 65
                     70
                                        75
tte tqt ttt cqt tqq aaa ctt aaa qaa ata aaq acc atc gaa qqa ttg
                                                                   288
Phe Cys Phe Arg Trp Lys Leu Lys Glu Ile Lys Thr Ile Glu Gly Leu
                 85
                                      90
                                                          95
ctc cag gat ctc gat agt cga gtt gaa agt gaa gaa gaa cgc aac tac
Leu Gln Asp Leu Asp Ser Arg Val Glu Ser Glu Glu Glu Arg Asn Tyr
                                                     110
```

Thr Val Tyr Ala Ile Ala Ser Gly Met Asn Leu Asp Gln Lys Leu Ser

105

	aat Asn															384
	gta Val 130															432
	agt Ser			-			_		_						,	480
	caa Gln															528
	ggc Gly							-								576
_	ccg Pro				-		-					-		_		624
	cgt Arg 210		-	-				-	-				-	-	-	672
	acc Thr	-				-										720
	ata Ile		-			_						-		_		768
	ttc Phe															816
-	ttc Phe			-				-	_				-			864
	gct Ala 290	-	_			-				-	-					912

-	_		-	gag Glu		-	_				-				-	960
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	1> 3															
	2> Pl		ahil:	a mei	anor	7 a c + i										
\Z.I.	J - D.	.030	,,,,,,,	a me.	Larro	gas c										
	0> 1									_	_	_			_	
Met 1	Asp	Ser	Arg	Arg 5	Lys	Val	Arg	Ser	G1u 10	Asn	Leu	Tyr	Lys	Thr 15	Tyr	
Trp	Leu	Tyr	Trp 20	Arg	Leu	Leu	Gly	Val 25	Glu	Gly	Asp	Tyr	Pro 30	Phe	Arg	
Arg	Leu	Va1 35	Asp	Phe	Thr	Ile	Thr 40	Ser	Phe	Ile	Thr	Ile 45	Leu	Phe	Pro	
Va1	His 50	Leu	Ile	Leu	Gly	Met 55	Tyr	Lys	Lys	Pro	Gln 60	Ile	Gln	Val	Phe	
Arg 65		Leu	His	Phe	Thr 70	Ser	Glu	Cys	Leu	Phe 75	Cys	Ser	Tyr	Lys	Phe 80	
Phe	Cys	Phe	Arg	Trp 85	Lys	Leu	Lys	Glu	Ile 90	Lys	Thr	Ile	Glu	Gly 95	Leu	
Leu	Gln	Asp	Leu 100	Asp	Ser	Arg	Val	Glu 105	Ser	Glu	Glu	Glu	Arg 110		Tyr	

- Phe Asn Gln Asn Pro Ser Arg Val Ala Arg Met Leu Ser Lys Ser Tyr
 115 120 125
 - Leu Val Ala Ala Ile Ser Ala Ile Ile Thr Ala Thr Val Ala Gly Leu 130 \$135\$

 - Phe Gln Ala Thr Ala Ala Ile Tyr Trp Ile Ser Phe Ser Tyr Gln Ala $165 \hspace{1.5cm} 170 \hspace{1.5cm} 175$
 - Ile Gly Ser Ser Leu Leu Ile Leu Glu Asn Leu Ala Asn Asp Ser Tyr \$180\$
 - Pro Pro Ile Thr Phe Cys Val Val Ser Gly His Val Arg Leu Leu Ile 195 \$200\$
 - Met Arg Leu Ser Arg Ile Gly His Asp Val Lys Leu Ser Ser Glu 210 215 220
 - Asn Thr Arg Lys Leu Ile Glu Gly Ile Gln Asp His Arg Lys Leu Met 225 230 235 240
 - Lys Ile Ile Arg Leu Leu Arg Ser Thr Leu His Leu Ser Gln Leu Gly \$245\$
 - Gln Phe Leu Ser Ser Gly Ile Asn Ile Ser Ile Thr Leu Ile Asn Ile 260 \$265\$
 - Leu Phe Phe Ala Glu Asn Asn Phe Ala Met Leu Tyr Tyr Ala Val Phe \$275\$ \$280\$ \$285\$
 - Phe Ala Ala Met Leu Ile Glu Leu Phe Pro Ser Cys Tyr Tyr Gly Ile 290 295 300
 - Leu Met Thr Met Glu Phe Asp Lys Leu Pro Tyr Ala Ile Phe Ser Ser 305 \$310\$
 - Asn Trp Leu Lys Met Asp Lys Arg Tyr Asn Arg Ser Leu Ile Ile Leu 325 330 335
 - Met Gln Leu Thr Leu Val Pro Val Asn Ile Lys Ala Gly Gly Ile Val 340 345 350
 - Gly Ile Asp Met Ser Ala Phe Phe Ala Thr Val Arg Met Ala Tyr Ser 355 360 365

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or the or the second

<211 <212	0> 13 l> 13 2> Di 3> Di	L40 NA	phila	a mel	lano	gast∈	er									
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atg	-	tta	aaa Lys			-		-	-	-	-			-		48
			tat Tyr 20								-				-	96
	-	-	ttg Leu	-	-						-					144
			ctg Leu								-					192
-	-	-	ggt Gly				_	-	-	-			-	_		240
			tgt C ys													288
			aaa Lys 100		-	-	-		-							336

Phe Tyr Thr Leu Ala Leu Ser Phe Arg Val

115

gag ttt ttc aat caa aat acg aga cgt gag gcg aat ttc att tgg aaa Glu Phe Phe Asn Gln Asn Thr Arg Arg Glu Ala Asn Phe Ile Trp Lys

	ttc Phe 130															432
	t ctt L Leu															480
	c gat c Asp															528
	a att n Ile			-	-	_				_		_	-		-	576
	e tat r Tyr												-	-		624
	g gcg 1 Ala 210	-	-	_	-	-							-			672
	c tta r Leu 5															720
	a atg ı Met															768
	e gge u Gly															816
	c att n Ile				-	-				-						864
-	g tac 1 Tyr 290			_	_		-	-			_	-	-			912
	c acc y Thr	_					_		_	_	Thr					960

	agt Ser															1008
	ttc Phe															1056
-	att Ile				_		-			-						1104
	tcc Ser 370				-	-	_	_	_	-	taa					1140
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	0> 14 Asp		Lys	Pro 5	Arg	Val	Ile	Arg	Ser 10	Glu	Asp	Ile	Tyr	Arg 15	Thr	
Tyr	Trp	Leu	Tyr 20	Trp	His	Leu	Leu	Gly 25	Leu	Glu	Ser	Asn	Phe 30	Phe	Leu	
Asn	Arg	Leu 35	Leu	Asp	Leu	Val	Ile 40	Thr	Ile	Phe	Val	Thr 45	Ile	Trp	Tyr	
Pro	Ile 50	His	Leu	Ile	Leu	Gly 55	Leu	Phe	Met	Glu	Arg 60	Ser	Leu	Gly	Asp	
Val 65	Cys	Lys	Gly	Leu	Pro 70	Ile	Thr	Ala	Ala	Cys 75	Phe	Phe	Ala	Ser	Phe 80	
Lys	Phe	Ile	Cys	Phe 85	Arg	Phe	Lys	Leu	Ser 90	Glu	Ile	Lys	Glu	Ile 95	Glu	
Ile	Leu	Phe	Lys 100	Glu	Leu	Asp	Gln	Arg 105	Ala	Leu	Ser	Arg	Glu 110	Glu	Cys	
Glu	Phe	Phe	Asn	Gln	Asn	Thr	Arg	Arg	Glu	Ala	Asn	Phe	Ile	Trp	Lys	

- Ser Phe Ile Val Ala Tyr Gly Leu Ser Asn Ile Ser Ala Ile Ala Ser 130 135 140
- Val Leu Phe Gly Gly His Lys Leu Leu Tyr Pro Ala Trp Phe Pro 145 150 150 155
- Tyr Asp Val Gln Ala Thr Glu Leu Ile Phe Trp Leu Ser Val Thr Tyr \$165\$ \$170\$ \$175\$
- Gln Ile Ala Gly Val Ser Leu Ala Ile Leu Gln Asn Leu Ala Asn Asp \$180\$
- Ser Tyr Pro Pro Met Thr Phe Cys Val Val Ala Gly His Val Arg Leu 195 200 205
- Leu Ala Met Arg Leu Ser Arg Ile Gly Gln Gly Pro Glu Glu Thr Ile 210 215 220
- Tyr Leu Thr Gly Lys Gln Leu Ile Glu Ser Ile Glu Asp His Arg Lys 225 230 235 240
 - Leu Met Lys Ile Val Glu Leu Leu Arg Ser Thr Met Asn Ile Ser Gln \$245\$
 - Leu Gly Gln Phe Ile Ser Ser Gly Val Asn Ile Ser Ile Thr Leu Val \$260\$ \$265\$
 - Asn Ile Leu Phe Phe Ala Asp Asn Asn Phe Ala Ile Thr Tyr Tyr Gly 275 280 285
 - Val Tyr Phe Leu Ser Met Val Leu Glu Leu Phe Pro Cys Cys Tyr Tyr 290 295 300
 - Gly Thr Leu Ile Ser Val Glu Met Asn Gln Leu Thr Tyr Ala Ile Tyr 305 \$310\$ 315 \$320
 - Ser Ser Asn Trp Met Ser Met Asn Arg Ser Tyr Ser Arg Ile Leu Leu $325 \hspace{1.5cm} 330 \hspace{1.5cm} 335$
 - Ile Phe Met Gln Leu Thr Leu Ala Glu Val Gln Ile Lys Ala Gly Gly \$340\$ \$340\$ \$345\$
 - Met Ile Gly Ile Gly Met Asn Ala Phe Phe Ala Thr Val Arg Leu Ala \$355\$
 - Tyr Ser Phe Phe Thr Leu Ala Met Ser Leu Arg 370 375

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	> 15															48
			atc													40
met 1	vaı	TTe	Ile	Asp 5	ser	Leu	ser	PHE	10	Arg	FIO	FIIG	пр	15	СУБ	
1				,					10					13		
ata	cas	++ a	ctg	at a	cca	act	ttc	ttc	aad	gat	tcc	tca	cat	cct	atc	96
			Leu													
1100	my	Lou	20	· u.				25	2,0				30			
caq	ctq	tac	gtg	gtg	ttg	ctg	cac	atc	ctg	gtc	acc	ttg	tgg	ttt	cca	144
			Val													
		35					40					45				
ctg	cat	ctg	ctg	ctg	cat	ctt	ctg	cta	ctt	cca	tct	acc	gct	gag	ttc	192
Leu	His	Leu	Leu	Leu	His	Leu	Leu	Leu	Leu	Pro	Ser	Thr	Ala	Glu	Phe	
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			ctg													240
	Lys	Asn	Leu	Thr		Ser	Leu	Thr	Cys	75	Ala	Cys	ser	Leu	FÀ2	
65					70					/5					80	
	-+ ~	~~~	cac	++~	+ > +	000	++~	200	C2.0	2++	ata	722	atc	maa	tca	288
			His													200
птэ	vai	nia	1113	85	1 7 1	1123	Бец	110	90	110		014		95	001	
cta	atc	gag	caa	tta	gac	aca	ttt	att	qcc	agc	gaa	cag	gag	cat	cgt	336
			Gln													
			100					105					110			
tac	tat	cgg	gat	cac	gta	cat	tgc	cat	gct	agg	cgc	ttt	aca	aga	tgt	384
Tyr	Tyr	Arg	Asp	His	Val	His	Cys	His	Ala	Arg	Arg	Phe	Thr	Arg	Cys	
		115					120					125				
			agc													432
Leu	Tyr	Ile	Ser	Phe	Gly	Met	Ile	Tyr	Ala	Leu	Phe	Leu	Phe	Gly	Val	

130 135 140

	gtt Val													480
	cca Pro		-	_	-									528
	tat Tyr	-	-		-	-			-		-		-	 576
	gat Asp													624
	ttg Leu 210													672
_	gtg Val				_	-	_	_	-			_		720
	ttg Leu													768
	ctg Leu													816
	tac Tyr													864
	gtg Val 290													912
	gcc Ala													960
	tcc Ser	-	-			-								1008

325 330 335

ctc atc ttt aca caa tta aca ctg gga aac cgg ggg tgg atc atc aag $\,$ 1056 Leu Ile Phe Thr Gln Leu Thr Leu Gly Asn Arg Gly Trp Ile Ile Lys $\,$ 340 $\,$ 340 $\,$

gca gga ggt ctt atc gag ctg aat ttg aat gcc ttt ttc gcc acc ctg $$\,^{\circ}$ 1104 Ala Gly Gly Leu Ile Glu Leu Asn Leu Asn Ala Phe Phe Ala Thr Leu $_{355}$ $_{360}$

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370 375 380

tag 1155

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<213> Drosophila melanogaster

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Met Arg Leu Leu Val Pro Thr Phe Phe Lys Asp Ser Ser Arg Pro Val \$20\$

Gln Leu Tyr Val Val Leu Leu His Ile Leu Val Thr Leu Trp Phe Pro 35 40 45

Phe Lys Asn Leu Thr Met Ser Leu Thr Cys Val Ala Cys Ser Leu Lys 65 70 75 80

His Val Ala His Leu Tyr His Leu Pro Gln Ile Val Glu Ile Glu Ser $85 \hspace{1.5cm} 90 \hspace{1.5cm} 95$

Leu Ile Glu Gln Leu Asp Thr Phe Ile Ala Ser Glu Gln Glu His Arg

Tyr Tyr Arg Asp His Val His Cys His Ala Arg Arg Phe Thr Arg Cys \$115\$ \$120\$ \$125\$

Leu Tyr Ile Ser Phe Gly Met Ile Tyr Ala Leu Phe Leu Phe Gly Val

130 135 140

Phe Val Gln Val Ile Ser Gly Asn Trp Glu Leu Leu Tyr Pro Ala Tyr 145 150 155

Phe Pro Phe Asp Leu Glu Ser Asn Arg Phe Leu Gly Ala Val Ala Leu \$165\$

Gly Tyr Gln Val Phe Ser Met Leu Val Glu Gly Phe Gln Gly Leu Gly 180 185 190

Asn Asp Thr Tyr Thr Pro Leu Thr Leu Cys Leu Leu Ala Gly His Val 195 \$200\$

His Leu Trp Ser Ile Arg Met Gly Gln Leu Gly Tyr Phe Asp Asp Glu $210 \ \ 215 \ \ \ 220$

Thr Val Val Asn His Gln Arg Leu Leu Asp Tyr Ile Glu Gln His Lys 225 230235235

Leu Leu Val Arg Phe His Asn Leu Val Ser Arg Thr Ile Ser Glu Val 245 250 255

Gln Leu Val Gln Leu Gly Gly Cys Gly Ala Thr Leu Cys Ile Ile Val 260 265 270

Ser Tyr Met Leu Phe Phe Val Gly Asp Thr Ile Ser Leu Val Tyr Tyr 275 280 285

Leu Val Phe Phe Gly Val Val Cys Val Gln Leu Phe Pro Ser Cys Tyr 290 295 300

Phe Ala Ser Glu Val Ala Glu Glu Leu Glu Arg Leu Pro Tyr Ala Ile 305 310 315 320

Phe Ser Ser Arg Trp Tyr Asp Gln Ser Arg Asp His Arg Phe Asp Leu \$325\$

Leu Ile Phe Thr Gln Leu Thr Leu Gly Asn Arg Gly Trp Ile Ile Lys $340 \hspace{1cm} 345 \hspace{1cm} 350$

Ala Gly Gly Leu Ile Glu Leu Asn Leu Asn Ala Phe Phe Ala Thr Leu \$355\$ \$360\$ \$365\$

Lys Met Ala Tyr Ser Leu Phe Ala Val Val Val Arg Ala Lys Gly Ile $370 \ \ 375 \ \ 380$

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			gag Glu													48
			gcc Ala 20													96
ttc Phe	gcc Ala	ttc Phe 35	gtg Val	ctg Leu	ccg Pro	gtg Val	act Thr 40	gcg Ala	atg Met	aat Asn	ctg Leu	atg Met 45	cag Gln	ttc Phe	gtc Val	144
Tyr	Leu 50	Leu	cgg Arg	Met	Trp	Gly 55	Asp	Leu	Pro	Ala	Phe 60	Ile	Leu	Asn	Met	192
			tcg Ser													240
			cgg Arg													288
			tcg Ser 100													336
ctg Leu	cgg Arg	agg Arg 115	gcg Ala	gaa Glu	cgg Arg	gag Glu	gct Ala 120	Arg	aac Asn	ctg Leu	gcc Ala	atc Ile 125	ctt Leu	aat Asn	ttg Leu	384
agt Ser	gcc Ala 130	Ser	ttc Phe	ctg Leu	gac Asp	att Ile 135	gtc Val	ggt Gly	gct Ala	ctg Leu	ttt Phe 140	ttc Phe	gaa Glu	tat Tyr	aaa Lys	432

			ggt Gly		-						-					480
	-		cca Pro			-	-		-			-				528
		_	gcc Ala 180		-		-		_	_	_		-	-		576
_			gtc Val	-			-		_	-				_	-	624
-	-	_	atc Ile	_	-			_		_				-		672
			gag Glu						_	-		-				720
			gtg Val	-					-				-		-	768
			gcg Ala 260													816
			tgt Cys													864
			tac Tyr													912
		-	aat Asn	-		-										960
			gtg Val					-		Thr			-			1008

ctc ctg atc ttc ttg atg caa aca cac ccg atg gag ata aga gtc 1056 Leu Leu Ile Phe Leu Met Gln Thr Gln His Pro Met Glu Ile Arg Val qqc aac qtt tac ccc atq aca ttq qcc atg ttc cag agt ctg ttg aat 1104 Gly Asn Val Tyr Pro Met Thr Leu Ala Met Phe Gln Ser Leu Leu Asn 355 360 365 geg tee tac tee tac ttt acc atg etg egt gge gte acc gge aaa tga 1152 Ala Ser Tyr Ser Tyr Phe Thr Met Leu Arg Gly Val Thr Gly Lys 370 375 <210> 18 <211> 383 <212> PRT <213> Drosophila melanogaster <400> 18 Met Thr Ile Glu Asp Ile Gly Leu Val Gly Ile Asn Val Arg Met Trp 10 Arg His Leu Ala Val Leu Tyr Pro Thr Pro Gly Ser Ser Trp Arg Lys 20 25 30 Phe Ala Phe Val Leu Pro Val Thr Ala Met Asn Leu Met Gln Phe Val 40 35 Tyr Leu Leu Arg Met Trp Gly Asp Leu Pro Ala Phe Ile Leu Asn Met 50 Phe Phe Phe Ser Ala Ile Phe Asn Ala Leu Met Arg Thr Trp Leu Val 65 70 Ile Ile Lys Arg Arg Gln Phe Glu Glu Phe Leu Gly Gln Leu Ala Thr 85 Leu Phe His Ser Ile Leu Asp Ser Thr Asp Glu Trp Gly Arg Gly Ile 100 105 Leu Arg Arg Ala Glu Arg Glu Ala Arg Asn Leu Ala Ile Leu Asn Leu 120 115 Ser Ala Ser Phe Leu Asp Ile Val Gly Ala Leu Phe Phe Glu Tyr Lys

Phe Pro Ile Gly Val Val Thr Phe Phe Leu Pro Ala His Pro Phe Gly

1.55

135

150

130

- Leu Ala Leu Pro Gly Val Ser Met Thr Ser Ser Pro Val Tyr Glu Val 165 170 175
- Ile Tyr Leu Ala Gln Leu Pro Thr Pro Leu Leu Leu Ser Met Met Tyr 180 185 190
- Met Pro Phe Val Ser Leu Phe Ala Gly Leu Ala Ile Phe Gly Lys Ala 195 200 205
- Met Leu Gln Ile Leu Val His Arg Leu Gly Gln Ile Gly Gly Glu Glu 210 215 220
- Gln Ser Glu Glu Glu Arg Phe Gln Arg Leu Ala Ser Cys Ile Ala Tyr 225 230 235 240
- His Thr Gln Val Met Arg Tyr Val Trp Gln Leu Asn Lys Leu Val Ala \$245\$
- Asn Ile Val Ala Val Glu Ala Ile Ile Phe Gly Ser Ile Ile Cys Ser 260 265 270
- Leu Leu Phe Cys Leu Asn Ile Ile Thr Ser Pro Thr Gln Val Ile Ser 275 280 285
- Ile Val Met Tyr Ile Leu Thr Met Leu Tyr Val Leu Phe Thr Tyr Tyr 290 295 300
- Asn Arg Ala Asn Glu Ile Cys Leu Glu Asn Asn Arg Val Ala Glu Ala 305 310 315 320
- Val Tyr Asn Val Pro Trp Tyr Glu Ala Gly Thr Arg Phe Arg Lys Thr 325 330 335
- Leu Leu Ile Phe Leu Met Gln Thr Gln His Pro Met Glu Ile Arg Val \$340\$ \$345\$
- Gly Asn Val Tyr Pro Met Thr Leu Ala Met Phe Gln Ser Leu Leu Asn 355 360 365
- Ala Ser Tyr Ser Tyr Phe Thr Met Leu Arg Gly Val Thr Gly Lys 370 375 380

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				gtc Val									144
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				atc Ile 70									240
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				aac Asn									336
				gca Ala									384
				tcg Ser									432
				tgg Trp 150									480

	ggc Gly	-				-			-		528
_	tgt Cys	_	-	-	-	-				-	576
	ctc Leu										624
	gcc Ala 210										672
	act Thr										720
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	att Ile										864
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	ggt Gly										960
	acc Thr										1008
	ttt Phe										1056

cca agt ctt ggt ttt gae tta atg ctc ttc agc tcg gtg agt tct ttc Pro Ser Leu Gly Phe Asp Leu Met Leu Phe Ser Ser Val Ser Ser Phe 355 360 cqt qtt ttq act ttt ttq tqc act qta gcc aat ttc cat aat gag gct 1152 Arg Val Leu Thr Phe Leu Cys Thr Val Ala Asn Phe His Asn Glu Ala 370 375 380 1158 cat tag His 385 <210> 20 <211> 385 <212> PRT <213> Drosophila melanogaster <400> 20 Met Ser Lys Gly Val Glu Ile Phe Tyr Lys Gly Gln Lys Ala Phe Leu 10 Asn Ile Leu Ser Leu Trp Pro Gln Ile Glu Arg Arg Trp Arg Ile Ile 25 20 His Gln Val Asn Tyr Val His Val Ile Val Phe Trp Val Leu Leu Phe 40 Asp Leu Leu Val Leu His Val Met Ala Asn Leu Ser Tyr Met Ser 55 Glu Val Val Lys Ala Ile Phe Ile Leu Ala Thr Ser Ala Gly His Thr 65 70 Thr Lys Leu Leu Ser Ile Lys Ala Asn Asn Val Gln Met Glu Glu Leu 90 85 Phe Arg Arg Leu Asp Asn Glu Glu Phe Arg Pro Arg Gly Ala Asn Glu 100 Glu Leu Ile Phe Ala Ala Ala Cys Glu Arg Ser Arg Lys Leu Arg Asp 120 115 Phe Tyr Gly Ala Leu Ser Phe Ala Ala Leu Ser Met Ile Leu Ile Pro 140 135

Leu Gly Glu Asn Thr Gly Ser Pro Ala Tyr Trp Leu Leu Tyr Cys Tyr \$165\$ \$170\$ \$170\$

Gln Cys Leu Ala Leu Ser Val Ser Cys Ile Thr Asn Ile Gly Phe Asp $180 \,$ $\,$ $185 \,$ $\,$ $\,$ $190 \,$

Ser Leu Cys Ser Ser Leu Phe Ile Phe Leu Lys Cys Gln Leu Asp Ile 195 200 205

Leu Ala Val Arg Leu Asp Lys Ile Gly Arg Leu Ile Thr Thr Ser Gly 210 215 220

Gly Thr Val Glu Gln Gln Leu Lys Glu Asn Ile Arg Tyr His Met Thr 225 \$230\$ 235 240

Ile Val Glu Leu Ser Lys Thr Val Glu Arg Leu Leu Cys Lys Pro Ile \$245\$

Ser Val Gln Ile Phe Cys Ser Val Leu Val Leu Thr Ala Asn Phe Tyr 260 265 270

Ala Ile Ala Val Leu Ser Asp Glu Arg Leu Glu Leu Phe Lys Tyr Val 275 280 285

Thr Tyr Gln Ala Cys Met Leu Ile Gln Ile Phe Ile Leu Cys Tyr Tyr $290 \\ \hspace{1.5cm} 295 \\ \hspace{1.5cm} 300 \\ \hspace{1.5cm}$

Ala Gly Glu Val Thr Gln Arg Ser Leu Asp Leu Pro His Glu Leu Tyr 305 \$310\$ 315 320

Lys Thr Ser Trp Val Asp Trp Asp Tyr Arg Ser Arg Arg Ile Ala Leu \$325\$ \$330\$

Leu Phe Met Gln Arg Leu His Ser Thr Leu Arg Ile Arg Thr Leu Asn \$340\$ \$350\$

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His 385

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	c ato												1008

130

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135

Ser Tyr Gly Ile Met Ser Leu Gly Ala Ala Ser Leu Ile Leu Ile Val

- Pro Cys Phe Asp Asn Phe Gly Glu Leu Pro Leu Ala Met Leu Glu Val 145 150 150 155
- Cys Ser Ile Glu Gly Trp Ile Cys Tyr Trp Ser Gln Tyr Leu Phe His 165 170 175
- Ser Ile Cys Leu Leu Pro Thr Cys Val Leu Asn Ile Thr Tyr Asp Ser 180 185 190
- Val Ala Tyr Ser Leu Leu Cys Phe Leu Lys Val Gln Leu Gln Met Leu 195 200 205
- Val Leu Arg Leu Glu Lys Leu Gly Pro Val Ile Glu Pro Gln Asp Asn 210 215 220
- Glu Lys Ile Ala Met Glu Leu Arg Glu Cys Ala Ala Tyr Tyr Asn Arg 225 $230 \qquad \qquad 235 \qquad \qquad 240$
- Ile Val Arg Phe Lys Asp Leu Val Glu Leu Phe Ile Lys Gly Pro Gly 245 250 255
- Ser Val Gln Leu Met Cys Ser Val Leu Val Leu Val Ser Asn Leu Tyr 260 265 270
- Lys Thr Cys Ile Tyr Gln Leu Val Met Leu Trp Gln Ile Phe Ile Ile 290 295 300
- Cys Tyr Ala Ser Asn Glu Val Thr Val Gln Ser Ser Arg Leu Cys His 305 310 315 320
- Ser Ile Tyr Ser Ser Gln Trp Thr Gly Trp Asn Arg Ala Asn Arg Arg 325 \$330\$
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- Thr Phe Asn Pro Thr Phe Ala Phe Ser Leu Glu Ala Phe Gly Ser Ile 355 360 365
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Leu	ıyı	Leu	ALG	85	nap	FIIG	БУЗ	ALY	90	110	nop	шys	1110	95	200	
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Leu	Met	Ser	Asn	Glu	Ala	Glu	Gln	Gly	Glu	Glu	Tyr	Ala	Glu	Ile	Leu	
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130

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135

Cys Phe Leu Leu Ala Trp Ala Leu Asn Ser Val Leu Pro Leu Val Arg

Phe Pro Cys Leu Phe Pro Trp Asn Ile His Ile Ile Arg Asn Tyr Val  $165 \hspace{1.5cm} 170 \hspace{1.5cm} 175$ 

Leu Ser Phe Ile Trp Ser Ala Phe Ala Ser Thr Gly Val Val Leu Pro 180 185 190

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Ala Phe Phe Lys Ile Ala Gln Tyr Lys Val Val Arg Phe Lys Gly Gly 210 215 220

Ser Leu Lys Glu Ser Gln Ala Thr Leu Asn Lys Val Phe Ala Leu Tyr 225 230 235 240

Gln Thr Ser Leu Asp Met Cys Asn Asp Leu Asn Gln Cys Tyr Gln Pro 245 250 255

Gly Tyr Leu Phe Ser Ile Thr Phe Ala Gln Thr Glu Gly Val Tyr Tyr 275 280 285

Ala Ser Phe Ile Ala Thr Ile Ile Ile Gln Ala Tyr Ile Tyr Cys Tyr 290 295 300

Cys Gly Glu Asn Leu Lys Thr Glu Ser Ala Ser Phe Glu Trp Ala Ile 305 \$310\$ \$315 \$320

Tyr Asp Ser Pro Trp His Glu Ser Leu Gly Ala Gly Gly Ala Ser Thr \$325\$

Ser Ile Cys Arg Ser Leu Leu Ile Ser Met Met Arg Ala His Arg Gly \$340\$ \$345\$

Phe Arg Ile Thr Gly Tyr Phe Phe Glu Ala Asn Met Glu Ala Phe Ser 355 360 365

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Ser

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					caa Gln											864
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Glu	Val 130	Leu	Gly	Trp	Gln	Arg 135	Leu	Cys	Tyr	Val	Ile 140	Glu	Ser	Gly	Leu
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Pro	Phe	Gln	Trp 180	His	Arg	Leu	Asp	Leu 185	His	Pro	Tyr	Thr	Phe 190	Trp	Phe
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His	Gln	His	Ile 260	Ile	Lys	Leu	Val	Gly 265	Lys	Ala	Asn	Arg	Ala 270	Phe	Asn
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Trp	Cys	Val	Ser	Gly 325	Thr	Leu	Val	Tyr	Thr 330	Gln	Ser	Val	Glu	Val 335	Ala
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		Asn Leu Thr	acc ttt gcg acc Thr Phe Ala Thr 75	
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-	-	_		_	gcg Ala									624
					aga Arg									672
	-	-	_	-	ctg Leu 230	 -	_			-		_		720
	_			_	ege Arg		-				_		-	768
					acc Thr									816
					agc Ser									864
					ccg Pro									912

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Lys	Asn	Leu 35	Tyr	Val	Phe	Tyr	Ser 40	Ile	Val	Ser	Asn	Leu 45	Leu	Val	Thr	
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Lys	Met 210	Leu	Tyr	Asn	Arg	Phe 215	Glu	Glu	Val	Gly	Leu 220	Asp	Pro	Ala	Arg
Asp 225	Ala	Glu	Lys	Asp	Leu 230	Glu	Ala	Суѕ	Ile	Thr 235	Asp	His	Lys	His	Ile 240
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                                     90
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Leu His Glu Ile Arg Ser Leu Leu Arg Leu Met Asp Ala Arg Ala Arg
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Ser Leu Phe Thr Ile Ile Ile Arg Met Arg Lys

375

115 120 125

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				cag Gln 245	-				-		-	-	-			768
-			-	agg Arg				_		-					-	816
				gtc Val												864
		-		gta Val		-	-		-			-	-			912
				ttc Phe	_	-	-		_				-		_	960

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					tgg Trp			_	_		_		_	_	-	1056
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Val	Thr 50	Val	Leu	Phe	Pro	Leu 55	Ser	Leu	Leu	Ala	Arg 60	Leu	Leu	Phe	Thr	
Thr 65	Asn	Met	Ala	Gly	Leu 70	Cys	Glu	Asn	Leu	Thr 75	Ile	Thr	Ile	Thr	Asp 80	
Ile	Val	Ala	Asn	Leu 85	Lys	Phe	Ala	Asn	Val 90	Tyr	Met	Val	Arg	Lys 95	Gln	

100 105 110

Leu Val Gly Asp Pro Glu Glu Ile Ser Ala Leu Arg Lys Glu Val Asn 115 120 125

Ile Ala Gln Gly Thr Phe Arg Thr Phe Ala Ser Ile Phe Val Phe Gly
130 135 140

Thr Thr Leu Ser Cys Val Arg Val Val Val Arg Pro Asp Arg Glu Leu 145 150 155 160

Leu Tyr Pro Ala Trp Phe Gly Val Asp Trp Met His Ser Thr Arg Asn 165 170 175

Tyr Val Leu Ile Asn Ile Tyr Gln Leu Phe Gly Leu Ile Val Gln Ala 180 185 190

Ile Gln Asn Cys Ala Ser Asp Ser Tyr Pro Pro Ala Phe Leu Cys Leu 195 \$200\$

Leu Thr Gly His Met Arg Ala Leu Glu Leu Arg Val Arg Arg Ile Gly 210 215 220

Cys Arg Thr Glu Lys Ser Asn Lys Gly Gln Thr Tyr Glu Ala Trp Arg 225  $\phantom{\bigg|}$  230  $\phantom{\bigg|}$  235  $\phantom{\bigg|}$  240

Glu Glu Val Tyr Gln Glu Leu Ile Glu Cys Ile Arg Asp Leu Ala Arg \$245\$ \$250\$ \$255\$

Val His Arg Leu Arg Glu Ile Ile Gln Arg Val Leu Ser Val Pro Cys 260 265 270

Met Ala Gln Phe Val Cys Ser Ala Ala Val Gln Cys Thr Val Ala Met  $275 \\ 280 \\ 285$ 

His Phe Leu Tyr Val Ala Asp Asp His Asp His Thr Ala Met Ile Ile 290 \$295\$

Ser Ile Val Phe Phe Ser Ala Val Thr Leu Glu Val Phe Val Ile Cys 305 310 315 320

Tyr Phe Gly Asp Arg Met Arg Thr Gln Ser Glu Ala Leu Cys Asp Ala 325 330 335

Phe Tyr Asp Cys Asn Trp Ile Glu Gln Leu Pro Lys Phe Lys Arg Glu
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Leu Leu Phe Thr Leu Ala Arg Thr Gln Arg Pro Ser Leu Ile Tyr Ala

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									tac Tyr						96
									aaa Lys						144
	_								gta Val	-			_	-	192
	_		-						cga Arg						240
									gga Gly 90						288

tot ttt aag tgc gcc ttc acc ttg att gga ttc aag aaa aga cag gaa

100 105 110

	aag Lys															384
	agg Arg 130					-		-	-	_						432
	ttg Leu										-	-				480
	ttt Phe	-			-	-		-		-						528
	gat Asp															576
	atg Met															624
_	atc Ile 210		_		_	-	_	-			-		_		_	672
	ctg Leu															720
	gag Glu															768
	gtt Val	-	-	-	-		-		-						-	816
	ctc Leu	_				-	_				_				_	864
	ttc Phe	_						-	-		_			-		912

290 295 300

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		_						_	-		gga Gly					1104
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Ser	Phe	Gly 35	Trp	Thr	Glu	Pro	Glu 40	Asn	Lys	Arg	Trp	Ile 45	Leu	Pro	Tyr	
Lys	Leu 50	Trp	Leu	Ala	Phe	Val 55	Asn	Ile	Val	Met	Leu 60	Ile	Leu	Leu	Pro	
Ile 65	Ser	Ile	Ser	Ile	Glu 70	Tyr	Leu	His	Arg	Phe 75	Lys	Thr	Phe	Ser	Ala 80	

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Ala	Lys	Val 115	Leu	Leu	Asp	Gln	Leu 120	Asp	Lys	Arg	Cys	Leu 125	Ser	Asp	Lys
Glu	Arg 130	Ser	Thr	Val	His	Arg 135	Tyr	Val	Ala	Met	Gly 140	Asn	Phe	Phe	Asp
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Tyr	Phe	Leu	Leu	Glu 165	Arg	Arg	His	Ala	Trp 170	Arg	Met	Tyr	Phe	Pro 175	Tyr
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Leu	Met	Thr 195	Glu	Ala	Ile	Tyr	Met 200	Asp	Leu	Cys	Thr	Asp 205	Val	Cys	Pro
Leu	Ile 210	Ser	Met	Leu	Met	Ala 215	Arg	Cys	His	Ile	Ser 220	Leu	Leu	Lys	Gln
Arg 225	Leu	Arg	Asn	Leu	Arg 230	Ser	Lys	Pro	Gly	Arg 235	Thr	Glu	Asp	Glu	Tyr 240
Leu	Glu	Glu	Leu	Thr 245	Glu	Cys	Ile	Arg	Asp 250	His	Arg	Leu	Leu	Leu 255	Asp
Tyr	Val	Asp	Ala 260	Leu	Arg	Pro	Val	Phe 265	Ser	Gly	Thr	Ile	Phe 270	Val	Gln
Phe	Leu	Leu 275	Ile	Gly	Thr	Val	Leu 280	Gly	Leu	Ser	Met	Ile 285	Asn	Leu	Met
Phe	Phe 290	Ser	Thr	Phe	Trp	Thr 295	Gly	Val	Ala	Thr	Cys 300	Leu	Phe	Met	Phe
Asp 305	Val	Ser	Met	Glu	Thr 310	Phe	Pro	Phe	Cys	Tyr 315	Leu	Cys	Asn	Met	Ile 320

Ile Asp Asp Cys Gln Glu Met Ser Asn Cys Leu Phe Gln Ser Asp Trp 325 330 335

Thr																
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Ser	Met 370	Gln	Thr	Asn	Leu	Ala 375	Met	Val	Lys	Leu	Ala 380	Phe	Ser	Val	Val	
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gct	tgg	ccc	ttg	gcg	gtt	ttt	cgg	tta	aat	cac	ata	ttc	tgg	cca	ttg	96
Ala	Trp	Pro	Leu 20	Ala	Val	Phe	Arg	Leu 25	Asn	His	Ile	Phe	Trp 30	Pro	Leu	
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Asp	Pro	Ser 35	Thr	Gly	Lys	Trp	Gly 40	Arg	Tyr	Leu	Asp	Lys 45	Val	Leu	Ala	
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Val	Ala 50	Met	Ser	Leu	Val	Phe 55	Met	Gln	His	Asn	Asp 60	Ala	Glu	Leu	Arg	
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Tyr 65																
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	-	aat Asn 115				-	-	-	-		-	-		-	384
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	-	gtt Val			_										480
		agc Ser		-											528
		ttg Leu													576
		gta Val 195													624
		att Ile	-				 -								672
_		ttg Leu			-	_		-	-						720
		aaa Lys													768
		cta Leu													816
	-	ttt Phe 275		_											864

		_	-		-	_	-			-		_		tac Tyr		912
	290					295					300					
						_	-						-	gaa Glu		960
305	urs	irp	GIU	GIII	310	neu	GIII	TYL	Ser	315	ASII	110	Jei	GIU	320	
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Leu	Arg	Leu	Leu	Lys 325	Leu	Ile	Asn	Leu	330	Ile	Glu	Met	Asn	Ser 335	Lys	
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Pro	Phe	Tyr	Val 340	Thr	Gly	Leu	Lys	Tyr 345	Phe	Arg	Val	Ser	150 350	Gln	Ala	
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Met 1	Val	Arg	IYL	5	FIO	MIG	rne	nia	10	GIŞ	GIII	шуз	741	15	пса	
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Asp	Pro	Ser 35		Gly	Lys	Trp	Gly 40	Arg	Tyr	Leu	Asp	Lys 45	Va1	Leu	Ala	
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Tyr 65	Leu	Arg	Phe	Glu	Ala 70	Ser	Asn	Arg	Asn	Leu 75	Asp	Ala	Phe	Leu	Thr 80
Gly	Met	Pro	Thr	Tyr 85	Leu	Ile	Leu	Val	Glu 90	Ala	Gln	Phe	Arg	Ser 95	Leu
His	Ile	Leu	Leu 100	His	Phe	Glu	Lys	Leu 105	Gln	Lys	Phe	Leu	Glu 110	Ile	Phe
Tyr	Ala	Asn 115	Ile	Tyr	Ile	Asp	Pro 120	Arg	Lys	Glu	Pro	Glu 125	Met	Phe	Arg
Lys	Val 130	Asp	Gly	Lys	Met	Ile 135	Ile	Asn	Arg	Leu	Val 140	Ser	Ala	Met	Tyr
Gly 145	Ala	Val	Ile	Ser	Leu 150	Tyr	Leu	Ile	Ala	Pro 155	Val	Phe	Ser	Ile	Ile 160
Asn	Gln	Ser	Lys	Asp 165	Phe	Leu	Tyr	Ser	Met 170	Ile	Phe	Pro	Phe	Asp 175	Ser
Asp	Pro	Leu	Tyr 180	Ile	Phe	Val	Pro	Leu 185	Leu	Leu	Thr	Asn	Val 190	Trp	Val
Gly	Ile	Val 195	Ile	Asp	Thr	Met	Met 200	Phe	Gly	Glu	Thr	Asn 205	Leu	Leu	Cys
Glu	Leu 210		Val	His	Leu	Asn 215	Gly	Ser	Tyr	Met	Leu 220	Leu	Lys	Arg	Asp
Leu 225	Gln	Leu	Ala	Ile	Glu 230	Lys	Ile	Leu	Val	Ala 235	Arg	Asp	Arg	Pro	His 240
Met	Ala	Lys	Gln	Leu 245	Lys	Val	Leu	Ile	Thr 250		Thr	Leu	Arg	Lys 255	Asn
Val	Ala	Leu	Asn 260		Phe	Gly	Gln	Gln 265		Glu	Ala	Gln	Tyr 270	Thr	Val
Arg	Val	Phe 275		Met	Phe	Ala	Phe 280		Ala	Gly	Leu	Leu 285		Ala	Leu
Ser	290		Ala	Tyr	Thr	Thr 295		Ser	Leu	Ser	Thr 300		Tyr	Tyr	Leu
Thr 305		Trp	Glu	ı Gln	1le 310		Glr	Туг	Ser	Thr 315		Pro	Ser	Glu	Asn 320

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Pro	Phe	Tyr	Val 340	Thr	Gly	Leu	Lys	Tyr 345	Phe	Arg	Val	Ser	Leu 350	Gln	Ala	
Gly	Leu	Lys 355	Val	Ser	Glu	Lys	Arg 360	Val	Gln	Asn	His	Phe 365	Thr	Val	Ser	
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	Gly					Gln					Ser				ttt Phe 80	240

						aat Asn						288
						tgg Trp 105						336
						tgc Cys						384
						agc Ser						432
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						ctg Leu						528
						gtg Val 185						576
						gat Asp						624
						gct Ala						672
	I1e					gag Glu		Ser				720
				Lys		atg Met	His				Arg	768
			Ile							Thr	cag Gln	816

	-	-			-	-	-			-				gtg Val		864
														gtt Val		912
		-	-	-					-			-		ctc Leu		960
-			-			-			-			-		aac Asn 335		1008
, ,	-	_	-	-							-			ctc Leu		1056
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Ser	Arg	Asp	Gly 20	Cys	Ile	Tyr	Leu	Tyr 25	Arg	Ala	Met	Lys	Phe 30	Ile	Gly	
Trp	Leu	Pro 35	Pro	Lys	Gln	Gly	Val 40	Leu	Arg	Tyr	Val	Tyr 45	Leu	Thr	Trp	

- Thr Leu Met Thr Phe Val Trp Cys Thr Thr Tyr Leu Pro Leu Gly Phe 50
- Leu Gly Ser Tyr Met Thr Gln Ile Lys Ser Phe Ser Pro Gly Glu Phe 65 70 75 80
- Leu Thr Ser Leu Gln Val Cys Ile Asn Ala Tyr Gly Ser Ser Val Lys \$85\$ 90 95
- Val Ala Ile Thr Tyr Ser Met Leu Trp Arg Leu Ile Lys Ala Lys Asn 100 105 110
- Ile Leu Asp Gln Leu Asp Leu Arg Cys Thr Ala Met Glu Glu Arg Glu \$115\$
- Lys Ile His Leu Val Val Ala Arg Ser Asn His Ala Phe Leu Ile Phe 130 135 140
- Thr Phe Val Tyr Cys Gly Tyr Ala Gly Ser Thr Tyr Leu Ser Ser Val 145 150 155 160
- Leu Ser Gly Arg Pro Pro Trp Gln Leu Tyr Asn Pro Phe Ile Asp Trp \$165\$
- His Asp Gly Thr Leu Lys Leu Trp Val Ala Ser Thr Leu Glu Tyr Met \$180\$
- Val Met Ser Gly Ala Val Leu Gln Asp Gln Leu Ser Asp Ser Tyr Pro \$195\$
- Leu Ile Tyr Thr Leu Ile Leu Arg Ala His Leu Asp Met Leu Arg Glu  $210 \ \ 215 \ \ 220$
- Arg Ile Arg Arg Leu Arg Ser Asp Glu Asn Leu Ser Glu Ala Glu Ser 225 230 235
- Tyr Glu Glu Leu Val Lys Cys Val Met Asp His Lys Leu Ile Leu Arg \$245\$
- Tyr Cys Ala Ile Ile Lys Pro Val Ile Gln Gly Thr Ile Phe Thr Gln  $260 \hspace{1.5cm} 265 \hspace{1.5cm} 270 \hspace{1.5cm}$
- Phe Leu Leu Ile Gly Leu Val Leu Gly Phe Thr Leu Ile Asn Val Phe 275 280 285
- Phe Phe Ser Asp Ile Trp Thr Gly Ile Ala Ser Phe Met Phe Val Ile 290 295 300

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				Ser					Leu					Cys	gtc Val	96
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	ggo															

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				ctg Leu												336
				ctc Leu												384
				att Ile												432
				gca Ala												480
tcg Ser	gcg Ala	atc Ile	ttc Phe	att Ile 165	gga Gly	agg Arg	cca Pro	ccg Pro	tac Tyr 170	caa Gln	aat Asn	tac Tyr	tac Tyr	cct Pro 175	ttt Phe	528
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				atg Met												624
				aat Asn			Leu					His			atc	672
ttc Phe 225	Ala	gag Glu	cgc Arg	ctt Leu	cga Arg 230	Arg	ttg Leu	gga Gly	act Thr	tat Tyr 235	Pro	tat Tyr	gaa Glu	ago Ser	cag Gln 240	720
gag Glu	cag Gln	aaa Lys	tat Tyr	gaa Glu 245	Arg	ttg Leu	gtt Val	cag Glr	tgo Cys 250	: Ile	caa Glr	gat Asp	cac His	aaa Lys 255	gta Val	768
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Ile	Leu	Arg	Phe 260	Val	Asp	Cys	Leu	Arg 265	Pro	Val	Ile	Ser	Gly 270	Thr	Ile	
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		gtc Val														912
		gcc Ala														960
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		tgg Trp														1056
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tcc Ser 385	Val	ttt Phe	act Thr	ctc Leu	gta Val 390	Lys	caa Gln	atg Met	aac Asn	ata Ile 395	Ser	gag Glu	aaa Lys	ctt Leu	gcc Ala 400	1200
		gaa Glu			Glu											1218
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			ı Arç	J Arq		Phe	e Pro	o Thi	Leu		r Thi	r Glı	n Sei	: Lys	s Asp	

- Ser Pro Val Arg Ser Arg Asp Ala Thr Leu Tyr Leu Leu Arg Cys Val 20 25 30
- Phe Leu Met Gly Val Arg Lys Pro Pro Ala Lys Phe Phe Val Ala Tyr 35 40 45
- Val Leu Trp Ser Phe Ala Leu Asn Phe Cys Ser Thr Phe Tyr Gln Pro
- Ile Gly Phe Leu Thr Gly Tyr Ile Ser His Leu Ser Glu Phe Ser Pro 65 70 75 80
- Gly Glu Phe Leu Thr Ser Leu Gln Val Ala Phe Asn Ala Trp Ser Cys 85 90 95
- Ser Thr Lys Val Leu Ile Val Trp Ala Leu Val Lys Arg Phe Asp Glu 100 105 110
- Ala Asn Asn Leu Leu Asp Glu Met Asp Arg Arg Ile Thr Asp Pro Gly
- Glu Arg Leu Gln Ile His Arg Ala Val Ser Leu Ser Asn Arg Ile Phe 130 135 140
- Phe Phe Phe Met Ala Val Tyr Met Val Tyr Ala Thr Asn Thr Phe Leu 145 150 155 160
- Ser Ala Ile Phe Ile Gly Arg Pro Pro Tyr Gln Asn Tyr Tyr Pro Phe 165 170 175
- Leu Asp Trp Arg Ser Ser Thr Leu His Leu Ala Leu Gln Ala Gly Leu 180 185 190
- Glu Tyr Phe Ala Met Ala Gly Ala Cys Phe Gln Asp Val Cys Val Asp 195 200 205
- Cys Tyr Pro Val Asn Phe Val Leu Val Leu Arg Ala His Met Ser Ile 210 215 220
- Phe Ala Glu Arg Leu Arg Leu Gly Thr Tyr Pro Tyr Glu Ser Gln 225 230 235 240
- Glu Gln Lys Tyr Glu Arg Leu Val Gln Cys Ile Gln Asp His Lys Val 245 250 255
- Ile Leu Arg Phe Val Asp Cys Leu Arg Pro Val Ile Ser Gly Thr Ile \$260\$

Pl	he	Val	Gln 275	Phe	Leu	Val	Val	Gly 280	Leu	Val	Leu	Gly	Phe 285	Thr	Leu	Ile	
A	sn	Ile 290	Val	Leu	Phe	Ala	Asn 295	Leu	Gly	Ser	Ala	Ile 300	Ala	Ala	Leu	Ser	
	he 05	Met	Ala	Ala	Val	Leu 310	Leu	Glu	Thr	Thr	Pro 315	Phe	Cys	Ile	Leu	Cys 320	
Α	.sn	Tyr	Leu	Thr	Glu 325	Asp	Cys	Tyr	Lys	Leu 330	Ala	Asp	Ala	Leu	Phe 335	Gln	
S	er	Asn	Trp	Ile 340	Asp	Glu	Glu	Lys	Arg 345	Tyr	Gln	Lys	Thr	Leu 350	Met	Tyr	
P	he	Leu	Gln 355	Lys	Leu	Gln	Gln	Pro 360	Ile	Thr	Phe	Met	Ala 365	Met	Asn	Val	
P	he	Pro 370		Ser	Val	Gly	Thr 375	Asn	Ile	Ser	Val	Thr 380	Lys	Phe	Ser	Phe	
	er 385	Val	Phe	Thr	Leu	Val 390		Gln	Met	Asn	Ile 395		Glu	Lys	Leu	Ala 400	
Ι	Lys	Ser	Glu	Met	Glu 405												
		۵. ۵															
		0> 3 1> 1															
		2> 0															
4	<21	3> 0	rosc	phil	a me	lanc	gast	er									
	<22 <22	0> 1> 0	CDS														
			(1)														
	~ ~ ~ ~		JOR 1		•												
		0>3			++/	o ctr	- 200	· cat	- 220	tat	cer	r ctr	ı aca	c aac	cat	ttg	48
	atg Met 1	Түз	r Pro	Arq	g Phe	E Let	ı Sei	Arq	g Ası	Tyr 10	Pro	Let	ı Alá	Lys	His	Leu	
	tto	tte	c gto	c acc	c aga	a tao	e te	e tti	t gg	e cto	g ct	g ggo	cte	g aga	a ttt	t ggc	96

Phe Phe Val Thr Arg Tyr Ser Phe Gly Leu Leu Gly Leu Arg Phe Gly

25

20

												gtg Val					144
												ttc Phe 60					192
1												ttt Phe					240
												atg Met					288
												ttg Leu					336
												gct Ala					384
												ttc Phe 140					432
:	att Ile 145	acc Thr	act Thr	gga Gly	gcc Ala	ttc Phe 150	gtt Val	ctg Leu	cgt Arg	tcc Ser	ctt Leu 155	tgg Trp	gaa Glu	atg Met	tgg Trp	gtg Val 160	480
ž	cgt Arg	cgt Arg	cat	cag Gln	gag Glu 165	Phe	aaa Lys	ttc Phe	gat Asp	atg Met 170	Pro	ttt Phe	cgc Arg	atg Met	ctg Leu 175	Phe	528
	cac His	gac Asp	ttt Phe	gcg Ala 180	His	ege Arg	atg Met	Pro	tgg Trp 185	Phe	cca Pro	gtt Val	ttc Phe	tat Tyr 190	Leu	tac Tyr	576
	tcc Ser	aca Thr	tgg Trp 195	Ser	ggc	cag Gln	gtc Val	act Thr 200	Val	tac Tyr	gcc Ala	ttt Phe	gct Ala 205	Gly	aca Thr	gat Asp	624
	ggt Gly	ttc Phe	Phe	ttt Phe	ggc Gly	r Phe	acc Thr	Leu	tac Tyr	atg Met	gcc Ala	tto Phe	Leu	cto Lev	caç Glr	gcc Ala	672

							gcc Ala								720
							tgt Cys							 -	768
							ata Ile		_	-				_	816
-	-				-		ttc Phe 280	-		-	-			-	864
	-	-		-			ttg Leu								912
						_	gtt Val		-	-				-	960
							act Thr								1008
_			-				act Thr		-	_			-	 	1056
-					_	-	gct Ala 360		-			-		 	1104
			-		_		cca Pro				-	-			1152
		_			-	_	gct Ala	_	_		_				1188

<210> 40 <211> 396 <212> PRT <213> Drosophila melanogaster

<400> 40

Met Tyr Pro Arg Phe Leu Ser Arg Asn Tyr Pro Leu Ala Lys His Leu 1  $\phantom{0}$  5  $\phantom{0}$  10  $\phantom{0}$  15

Phe Phe Val Thr Arg Tyr Ser Phe Gly Leu Leu Gly Leu Arg Phe Gly \$20\$

Lys Glu Gln Ser Trp Leu His Leu Leu Trp Leu Val Phe Asn Phe Val 35 40 45

Asn Leu Ala His Cys Cys Gln Ala Glu Phe Val Phe Gly Trp Ser His  $50 \hspace{1cm} 55 \hspace{1cm} 60$ 

Leu Arg Thr Ser Pro Val Asp Ala Met Asp Ala Phe Cys Pro Leu Ala 65 70 75 80

Cys Ser Phe Thr Thr Leu Phe Lys Leu Gly Trp Met Trp Trp Arg Arg 85 \$90\$ 95

Gln Glu Val Ala Asp Leu Met Asp Arg Ile Arg Leu Leu Ile Gly Glu 100 105 110

Gln Glu Lys Arg Glu Asp Ser Arg Arg Lys Val Ala Gln Arg Ser Tyr 115 120 125

Tyr Leu Met Val Thr Arg Cys Gly Met Leu Val Phe Thr Leu Gly Ser 130 135 140

Ile Thr Thr Gly Ala Phe Val Leu Arg Ser Leu Trp Glu Met Trp Val 145 150 150 155

Arg Arg His Gln Glu Phe Lys Phe Asp Met Pro Phe Arg Met Leu Phe \$165\$

His Asp Phe Ala His Arg Met Pro Trp Phe Pro Val Phe Tyr Leu Tyr 180 185 190

Ser Thr Trp Ser Gly Gln Val Thr Val Tyr Ala Phe Ala Gly Thr Asp 195 200 205

Gly Phe Phe Phe Gly Phe Thr Leu Tyr Met Ala Phe Leu Leu Gln Ala 210 215 220

Leu Arg Tyr Asp Ile Gln Asp Ala Leu Lys Pro Ile Arg Asp Pro Ser 225 230 235

1

Leu Arg Glu Ser Lys Ile Cys Cys Gln Arg Leu Ala Asp Ile Val Asp 250 Arg His Asn Glu Ile Glu Lys Ile Val Lys Glu Phe Ser Gly Ile Met 265 Ala Ala Pro Thr Phe Val His Phe Val Ser Ala Ser Leu Val Ile Ala 285 275 280 Thr Ser Val Ile Asp Ile Leu Leu Tyr Ser Gly Tyr Asn Ile Ile Arg 290 295 300 Tyr Val Val Tyr Thr Phe Thr Val Ser Ser Ala Ile Phe Leu Tyr Cys 315 305 310 Tyr Gly Gly Thr Glu Met Ser Thr Glu Ser Leu Ser Leu Gly Glu Ala 325 330 Ala Tyr Ser Ser Ala Trp Tyr Thr Trp Asp Arg Glu Thr Arg Arg Arg 345 340 Val Phe Leu Ile Ile Leu Arg Ala Gln Arg Pro Ile Thr Val Arg Val 355 360 365 Pro Phe Phe Ala Pro Ser Leu Pro Val Phe Thr Ser Val Ile Lys Phe 375 370 Thr Gly Ser Ile Val Ala Leu Ala Lys Thr Ile Leu 390 395 <210> 41 <211> 1158 <212> DNA <213> Drosophila melanogaster <220> <221> CDS <222> (1)..(1158) <223> DOR 49D.1 <400> 41 atg ttt gaa gac att cag cta atc tac atg aat atc aag ata ttg cga Met Phe Glu Asp Ile Gln Leu Ile Tyr Met Asn Ile Lys Ile Leu Arg

1 10.70

explain for

	tgg Trp														96
	ctg Leu	-								-					144
	aat Asn 50	-										_			192
	tgg Trp			-			-			-					240
-	aga Arg		-	-	-						-			-	288
	ctg Leu														336
	aag Lys			-											384
	aca Thr 130		-			 -			_			-	-	-	432
-	ctt Leu								-	-	-				480
-	aaa Lys														528
	tac Tyr			_	_			_	-		-	-	_		576
	ccg Pro														624

				ttg Leu												672
				cgc Arg												720
_		-		cag Gln 245	_	-					-	-				768
	_			atg Met	_				-	_	-	-		_		816
-		_		ctg Leu			_	_			-	-			-	864
				gtt Val												912
				tgg Trp												960
, ,	-			gcc Ala 325			-						-	-		1008
	_			atc Ile	-							-			-	1056
			_	ggc Gly			_									1104
		_		aca Thr						_	-		_	_	-	1152
	gga Gly															1158

<210>	42	
<211>	386	
<212>	PRT	
<213>	Drosophila	melanogaste

<400> 42

Met Phe Glu Asp Ile Gln Leu Ile Tyr Met Asn Ile Lys Ile Leu Arg 1  $\phantom{-}5\phantom{+}10\phantom{+}15\phantom{+}15$ 

Phe Trp Ala Leu Leu Tyr Asp Lys Asn Leu Arg Arg Tyr Val Cys Ile  $20 \hspace{1.5cm} 25 \hspace{1.5cm} 30$ 

Gly Leu Ala Ser Phe His Ile Phe Thr Gln Ile Val Tyr Met Met Ser  $35 \hspace{1.5cm} 40 \hspace{1.5cm} 45$ 

Thr Asn Glu Gly Leu Thr Gly Ile Ile Arg Asn Ser Tyr Met Leu Val\$50\$ \$60\$

Leu Trp Ile Asn Thr Val Leu Arg Ala Tyr Leu Leu Leu Ala Asp His  $65 \hspace{1.5cm} 70 \hspace{1.5cm} 75 \hspace{1.5cm} 80$ 

Asp Arg Tyr Leu Ala Leu Ile Gln Lys Leu Thr Glu Ala Tyr Tyr Asp \$85\$ 90 95

Leu Leu Asn Leu Asn Asp Ser Tyr Ile Ser Glu Ile Leu Asp Gln Val $100 \hspace{1.5cm} 105 \hspace{1.5cm} 110$ 

Asn Lys Val Gly Lys Leu Met Ala Arg Gly Asn Leu Phe Phe Gly Met 115 120 125

Leu Thr Ser Met Gly Phe Gly Leu Tyr Pro Leu Ser Ser Ser Glu Arg 130 135 140

Ala Leu Asn Phe Lys Thr His Phe Pro Phe Ala Val Leu Pro Phe Gly 145 150 150 155

Ser Lys Ile Pro Gly Leu Asn Glu Tyr Glu Ser Pro Tyr Tyr Glu Met 165 170 175

Trp Tyr Ile Phe Gln Met Leu Ile Thr Pro Met Gly Cys Cys Met Tyr 180 185 190

Ile Pro Tyr Thr Ser Leu Ile Val Gly Leu Ile Met Phe Gly Ile Val

Arg Cys Lys Ala Leu Gln His Arg Leu Arg Gln Val Ala Leu Lys His 210 215 220

Pro Tyr Gly Asp Arg Asp Pro Arg Glu Leu Arg Glu Glu Ile Ile Ala 225 230 235 Cys Ile Arg Tyr Gln Gln Ser Ile Ile Glu Tyr Met Asp His Ile Asn 245 250 Glu Leu Thr Thr Met Met Phe Leu Phe Glu Leu Met Ala Phe Ser Ala 260 265 Leu Leu Cys Ala Leu Leu Phe Met Leu Ile Ile Val Ser Gly Thr Ser 275 280 Gln Leu Ile Ile Val Cys Met Tyr Ile Asn Met Ile Leu Ala Gln Ile 300 Leu Ala Leu Tyr Trp Tyr Ala Asn Glu Leu Arg Glu Gln Asn Leu Ala 310 315 Val Ala Thr Ala Ala Tyr Glu Thr Glu Trp Phe Thr Phe Asp Val Pro 325 330 335 Leu Arg Lys Asn Ile Leu Phe Met Met Arg Ala Gln Arg Pro Ala 340 345 350 Ala Ile Leu Leu Gly Asn Ile Arg Pro Ile Thr Leu Glu Leu Phe Gln 355 360 Asn Leu Leu Asn Thr Thr Tyr Thr Phe Phe Thr Val Leu Lys Arg Val 370 375 380 Tyr Gly 385 <210> 43 <211> 1359 <212> DNA <213> Drosophila melanogaster <220> <221> CDS

<222> (1)..(1359)

<223> DOR 56E.1

<400> 43

atg gtt aac gct aaa cag ttt aac atg ttt aaa gtt aag gat ctg ttg 48

Met 1	Val	Asn	Ala	Lys 5	Gln	Phe	Asn	Met	Phe 10	Lys	Val	Lys	Asp	Leu 15	Leu	
	-					-	-						cac His 30	-	-	96
								-			-		aat Asn			144
													att Ile			192
													gaa Glu			240
													ttc Phe			288
													tat Tyr 110			336
					_		-	-					cga Arg	-	-	384
		-					_		-	-	-		cgg Arg		_	432
													acc Thr			480
				_	-		-						tca Ser			528
													gtg Val 190			576
gtg	cga	cgt	ggt	gag	gag	cat	ccc	att	ctg	cta	ttt	cag	ctg	ttt	ccc	624

Val	Arg	Arg 195	Gly	Glu	Glu	His	Pro 200	Ile	Leu	Leu	Phe	Gln 205	Leu	Phe	Pro	
												ttg Leu				672
	-	_		-			_	-			_	tgg Trp				720
							-			_	-	caa Gln				768
												tcc Ser				816
												caa Gln 285				864
	_	-		-	_							aaa Lys				912
												gat Asp				960
												aca Thr				1008
	_			-				_				ctt Leu				1056
												ttg Leu 365				1104
												gga Gly				1152
ttc	gaa	atg	cct	ttg	cag	aaa	atg	ctg	gtt	ttt	atg	atg	atg	cat	gcc	1200

Phe 385	Glu	Met	Pro	Leu	Gln 390	Lys	Met	Leu	Val	Phe 395	Met	Met	Met	His	Ala 400	
							gcc Ala									1248
							cta Leu									1296
_			-				cca Pro 440	-								1344
		ttt Phe	-													1359
<212 <212	)> 44 L> 45 2> PF 3> Dr	3 RT	ohila	a mei	Lanoq	gast	er									
	)> 44 Val		Ala	Lys 5	Gln	Phe	Asn	Met	Phe	Lys	Val	Lys	Asp	Leu 15	Leu	
Leu	Ser	Pro	Thr 20	Thr	Phe	Glu	Asp	Pro 25	Ile	Phe	Gly	Thr	His 30	Leu	Arg	
Tyr	Phe	Gln 35	Trp	Tyr	Gly	Tyr	Val 40	Ala	Ser	Lys	Asp	Gln 45	Asn	Arg	Pro	
Leu	Leu 50	Ser	Leu	Ile	Arg	Cys 55	Thr	Ile	Leu	Thr	Ala 60	Ser	Ile	Trp	Leu	
Ser 65	Cys	Ala	Leu	Met	Leu 70		Arg	Val	Phe	Arg 75	Gly	Tyr	Glu	Asn	Leu 80	
Asn	Asp	Gly	Ala	Thr 85	Ser	Tyr	Ala	Thr	Ala 90	Val	Gln	Tyr	Phe	Ala 95	Val	
Ser	Ile	Ala	Met	Phe	Asn	Ala	Tyr	Val		Arg	Asp	Arg	Tyr 110		Leu	

115 120 125

His	Ser 130	Asp	Ile	Gln	Asn	Leu 135	Met	His	Glu	Ala	Asp 140	Asn	Arg	Glu	Met
Glu 145	Leu	Leu	Val	Ala	Thr 150	Gln	Ala	Tyr	Thr	Arg 155	Thr	Ile	Thr	Leu	Leu 160
Ile	Trp	Ile	Pro	Ser 165	Val	Ile	Ala	Gly	Leu 170	Met	Ala	Tyr	Ser	Asp 175	Cys
Ile	Tyr	Arg	Ser 180	Leu	Phe	Leu	Pro	Lys 185	Ser	Val	Phe	Asn	Val 190	Pro	Ala
Val	Arg	Arg 195	Gly	Glu	Glu	His	Pro 200	I1e	Leu	Leu	Phe	Gln 205	Leu	Phe	Pro
Phe	Gly 210	Glu	Leu	Cys	Asp	Asn 215	Phe	Val	Val	Gly	Tyr 220	Leu	Gly	Pro	Trp
Tyr 225	Ala	Leu	Gly	Leu	Gly 230	Ile	Thr	Ala	Ile	Pro 235	Leu	Trp	His	Thr	Phe 240
Ile	Thr	Cys	Leu	Met 245	Lys	Tyr	Val	Asn	Leu 250	Lys	Leu	Gln	Ile	Leu 255	Asn
Lys	Arg	Val	Glu 260	Glu	Met	Asp	Ile	Thr 265	Arg	Leu	Asn	Ser	Lys 270	Leu	Val
Ile	Gly	Arg 275	Leu	Thr	Ala	Ser	Glu 280	Leu	Thr	Phe	Trp	Gln 285	Met	Gln	Leu
Phe	Lys 290	Glu	Phe	Val	Lys	Glu 295	Gln	Leu	Arg	Ile	Arg 300	Lys	Phe	Val	Gln
Glu 305	Leu	Gln	Tyr	Leu	Ile 310	Cys	Val	Pro	Val	Met 315	Ala	Asp	Phe	Ile	Ile 320
Phe	Ser	Val	Leu	Ile 325	Cys	Phe	Leu	Phe	Phe 330	Ala	Leu	Thr	Val	Gly 335	Val
Pro	Ser	Lys	Met 340	Asp	Tyr	Phe	Phe	Met 345	Phe	Ile	Tyr	Leu	Phe 350	Val	Met
Ala	Gly	Ile 355	Leu	Trp	Ile	Tyr	His 360	Trp	His	Ala	Thr	Leu 365	Ile	Val	Glu
Cys	His	Asp	Glu	Leu	Ser	Leu	Ala	Tyr	Phe	Ser	Cys	Gly	Trp	Tyr	Asn

Phe Glu Met Pro Leu Gln Lys Met Leu Val Phe Met Met His Ala 385 390 395 400

Gln Arg Pro Met Lys Met Arg Ala Leu Leu Val Asp Leu Asn Leu Arg 405 410 415

Thr Phe Ile Asp Val Arg Leu Leu Thr Ala Asn Ser Ile Leu Asp Leu \$420\$

Ser Asn Ser Ser Leu Ser Phe Pro Asp Trp Pro Trp Ser Leu Gln Leu 435 440 445

Leu Gln Phe Ala Ala 450

<210> 45

<211> 1278

<212> DNA

<213> Drosophila melanogaster

<220>

<221> CDS

<222> (1)..(1278)

<223> DOR 69F.1

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Met Gln Leu His Asp His Met Lys Tyr Ile Asp Leu Gly Cys Lys Met
1 5 10 15

- gca tgc ata cca aga tat caa tgg aaa gga cgc cct act gaa aga cag 96 Ala Cys Ile Pro Arg Tyr Gln Trp Lys Gly Arg Pro Thr Glu Arg Gln 20 25 30
- ttc tac gct tcg gag caa agg ata gtg ttc ctt ctt gga acc att tgc  $\,$  144 Phe Tyr Ala Ser Glu Gln Arg Ile Val Phe Leu Leu Gly Thr Ile Cys  $\,$  45  $\,$
- cag ata ttc cag att act gga gtg ctt atc tat tgg tat tgc aat ggc  $\,$  192 Gln Ile Phe Gln Ile Thr Gly Val Leu Ile Tyr Trp Tyr Cys Asn Gly  $\,$  50  $\,$  60
- cgt ctt gcc acg gaa acg ggc acc ttt gtg gca caa tta tct gaa atg 240 Arg Leu Ala Thr Glu Thr Gly Thr Phe Val Ala Gln Leu Ser Glu Met

COUNTRY, DIMENO

65			70			75			80	
		tgt Cys 85								288
		cgc Arg								336
		aga Arg								384
		atg Met								432
		tac Tyr								480
		gag Glu 165								528
		tgg Trp								576
		ata Ile								624
		aat Asn								672
		ata Ile								720
		aag Lys 245								768
		ggc Gly								816

								gcc Ala				864
								gcc Ala				912
		-						gtc Val				960
	_			_	-		-	ggt Gly 330	_		-	1008
								ttg Leu				1056
								ttc Phe				1104
								cta Leu				1152
								tgt Cys				1200
								ttc Phe 410			gag Glu	1248
-			-	_	cgc Arg							1278

<210> 46 <211> 426 <212> PRT <213> Drosophila melanogaster

<400	<400> 46														
Met 1	Gln	Leu	His	Asp 5	His	Met	Lys	Tyr	Ile 10	Asp	Leu	Gly	Cys	Lys 15	Met
Ala	Cys	Ile	Pro 20	Arg	Tyr	Gln	Trp	Lys 25	Gly	Arg	Pro	Thr	Glu 30	Arg	Gln
Phe	Tyr	Ala 35	Ser	Glu	Gln	Arg	Ile 40	Val	Phe	Leu	Leu	Gly 45	Thr	Ile	Cys
Gln	Ile 50	Phe	Gln	Ile	Thr	Gly 55	Val	Leu	Ile	Tyr	Trp 60	Tyr	Cys	Asn	Gly
Arg 65	Leu	Ala	Thr	Glu	Thr 70	Gly	Thr	Phe	Val	Ala 75	Gln	Leu	Ser	Glu	Met 80
Cys	Ser	Ser	Phe	Cys 85	Leu	Thr	Phe	Val	Gly 90	Phe	Cys	Asn	Val	Tyr 95	Ala
Ile	Ser	Thr	Asn 100	Arg	Asn	Gln	Ile	Glu 105	Thr	Leu	Leu	Glu	Glu 110	Leu	His

Gln Ile Tyr Pro Arg Tyr Arg Lys Asn His Tyr Arg Cys Gln His Tyr 

Phe Asp Met Ala Met Thr Ile Met Arg Ile Glu Phe Leu Phe Tyr Met 

Ile Leu Tyr Val Tyr Tyr Asn Ser Ala Pro Leu Trp Val Leu Leu Trp 

Glu His Leu His Glu Glu Tyr Asp Leu Ser Phe Lys Thr Gln Thr Asn 

Thr Trp Phe Pro Trp Lys Val His Gly Ser Ala Leu Gly Phe Gly Met 

Ala Val Leu Ser Ile Thr Val Gly Ser Phe Val Gly Val Gly Phe Ser 

Ile Val Thr Gln Asn Leu Ile Cys Leu Leu Thr Phe Gln Leu Lys Leu 

His Tyr Asp Gly Ile Ser Ser Gln Leu Val Ser Leu Asp Cys Arg Arg 

Pro Gly Ala His Lys Glu Leu Ser Ile Leu Ile Ala His His Ser Arg 

- Ile Leu Gln Leu Gly Asp Gln Val Asn Asp Ile Met Asn Phe Val Phe
  260 265 270
- Gly Ser Ser Leu Val Gly Ala Thr Ile Ala Ile Cys Met Ser Ser Val 275 280 285
- Ser Ile Met Leu Leu Asp Leu Ala Ser Ala Phe Lys Tyr Ala Ser Gly 290 295 300
- Leu Val Ala Phe Val Leu Tyr Asn Phe Val Ile Cys Tyr Met Gly Thr 305 310 315 320
- Glu Val Thr Leu Ala Arg Ile Lys Val Gly Asn Met Gly Gln Ile Arg 325 330 335
- Gln Pro Arg Phe Arg Ala Gly Trp Asn Leu Arg Thr Thr Leu Ser Ile \$340\$ \$345\$ \$350
- Leu Thr Ala Phe Cys Val Trp Arg Cys Phe His Glu Glu Asp Leu Tyr 355 360 365
- Pro Thr Phe Arg Arg Ala Phe Phe Leu Leu Gly Asn Phe Cys Leu Ala 370 375 380
- Tyr Gln Cys Ile Gly Val Ile Ile Asp Cys Ile Asp Trp Phe Ile Tyr 385 390 395 400
- Gly Arg Lys Ala Val Asp Thr Gln Arg Phe Val Ala Glu Ile Ser Glu \$405\$ \$410\$
- Ala Thr Gly Ala Arg Arg Ser Trp Ile Phe 420 425
- <210> 47
- <211> 1242
- <212> DNA
- <213> Drosophila melanogaster
- <220>
- <221> CDS
- <222> (1)..(1242)
- <223> DOR 69F.2
- <400> 47
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Met 1	Gln	Leu	Glu	Asp 5	Phe	Met	Arg	Tyr	Pro 10	Asp	Leu	Val	Cys	Gln 15	Ala	
				aga Arg												96
				gca Ala												144
				aat Asn												192
				gat Asp												240
				ggt Gly 85												288
				aag Lys												336
				cta Leu												384
				acg Thr												432
				tac Tyr												480
				aac Asn 165												528
				tgg Trp												576
aca	atc	acc	tat	caa	atc	ttt	tca	tac	caa	acc	aat	atq	tgc	qtc	aat	624

Ala	Val	Ala 195	Cys	Gln	Ile	Phe	Ser 200	Cys	Gln	Thr	Asn	Met 205	Cys	Val	Asn	
				ttt Phe												672
				ttg Leu												720
				gat Asp 245												768
_				gcc Ala		_	-		-	-						816
				tcg Ser												864
				ttc Phe												912
				atc Ile												960
				acg Thr 325												1008
				ggc Gly											ctg Leu	1056
				acg Thr									Lys		gca Ala	1104
							Met					Ser			aca Thr	1152
taa	cat	tta	tta	ttc	aat	ttt	aat	tca	tgt	gtt	ggc	ttt	cag	aca	ttg	1200

Trp His Leu Leu Phe Asn Phe Asn Ser Cys Val Gly Phe Gln Thr Leu 385 390 395 400

aag ttt toa tat caa atg ttt acc tgt gtg cgg tcc ctt aaa Lys Phe Ser Tyr Gln Met Phe Thr Cys Val Arg Ser Leu Lys 405 1242

<210> 48 <211> 414 <212> PRT <213> Drosophila melanogaster

<213> Drosophila melanogaste

<400> 48

Ala Gln Leu Pro Arg Tyr Thr Trp Asn Gly Arg Arg Ser Leu Glu Val  $20 \hspace{1.5cm} 25 \hspace{1.5cm} 30$ 

Lys Arg Asn Leu Ala Lys Arg Ile Ile Phe Trp Leu Gly Ala Val Asn 35 40 45

Leu Val Tyr His Asn Ile Gly Cys Val Met Tyr Gly Tyr Phe Gly Asp 50 55 60

Gly Arg Thr Lys Asp Pro Ile Ala Tyr Leu Ala Glu Leu Ala Ser Val  $_{\rm 65}$   $_{\rm 70}$   $_{\rm 75}$ 

Ala Ser Met Leu Gly Phe Thr Ile Val Gly Thr Leu Asn Leu Trp Lys

Met Leu Ser Leu Lys Thr His Phe Glu Asn Leu Leu Asn Glu Phe Glu 100 105 110

Glu Leu Phe Gln Leu Ile Lys His Arg Ala Tyr Arg Ile His His Tyr 115 120 125

Gln Glu Lys Tyr Thr Arg His Ile Arg Asn Thr Phe Ile Phe His Thr 130 135 140

Ser Ala Val Val Tyr Tyr Asn Ser Leu Pro Ile Leu Leu Met Ile Arg 145 150 155 160

Glu His Phe Ser Asn Ser Gln Gln Leu Gly Tyr Arg Ile Gln Ser Asn 165 170 175

Thr Trp Tyr Pro Trp Gln Val Gln Gly Ser Ile Pro Gly Phe Phe Ala

Ala	Val	Ala	Cys	Gln	Ile	Phe	Ser	Cys	Gln	Thr	Asn	Met	Cys	Val	Asn
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His Phe Asp Gly Leu Ala Arg Gln Leu Glu Thr Ile Asp Ala Arg Asn 225 230 235

Pro His Ala Lys Asp Gln Leu Lys Tyr Leu Ile Val Tyr His Thr Lys \$245\$

Leu Leu Asn Leu Ala Asp Arg Val Asn Arg Ser Phe Asn Phe Thr Phe 260 265 270

Leu Ile Ser Leu Ser Val Ser Met Ile Ser Asn Cys Phe Leu Ala Phe 275 280 285

Ser Met Thr Met Phe Asp Phe Gly Thr Ser Leu Lys His Leu Leu Gly 290 295 300

Leu Leu Leu Phe Ile Thr Tyr Asn Phe Ser Met Cys Arg Ser Gly Thr 305 \$310\$

His Leu Ile Leu Thr Ser Gly Lys Val Leu Pro Ala Ala Phe Tyr Asn \$325\$

Asn Trp Tyr Glu Gly Asp Leu Val Tyr Arg Arg Met Leu Leu Ile Leu 340 345 350

Met Met Arg Ala Thr Lys Pro Tyr Met Trp Lys Thr Tyr Lys Leu Ala 355 360 365

Pro Val Ser Ile Thr Thr Tyr Met Ala Val Ser Phe Ser Leu Leu Thr 370 375 380

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155

150

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		gaa Glu								720
		gtt Val 245								768
		ata Ile								816
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		gtt Val								912
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		tcg Ser 325								1008
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Tyr	Gly	His	Ile 20	Pro	Met	Gly	Glu	Glu 25	Ser	Lys	Arg	Asn	Lys 30	Leu	Ile	
Phe	His	Ile 35	Val	Phe	Trp	Ser	Asn 40	Val	Ile	Asn	Leu	Ser 45	Phe	Val	Gly	
Leu	Phe 50	Glu	Ser	Ile	Tyr	Val 55	Tyr	Ser	Ala	Phe	Met 60	Asp	Asn	Lys	Phe	
Leu 65	Glu	Ala	Val	Thr	Ala 70	Leu	Ser	Tyr	Ile	Gly 75	Phe	Val	Thr	Val	Gly 80	
Met	Ser	Lys	Met	Phe 85	Phe	Ile	Arg	Trp	Lys 90	Lys	Thr	Ala	Ile	Thr 95	Glu	
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Glu	Arg	Tyr 115	Asn	Leu	Pro	Met	Tyr 120	Leu	Gly	Thr	Cys	Ser 125	Arg	Ile	Ser	
Ļeu	Ile 130	Tyr	Ser	Leu	Leu	Tyr 135	Ser	Val	Leu	Ile	Trp 140	Thr	Phe	Asn	Leu	
Phe	Cys	Val	Met	Glu	Tyr	Trp	Val	Tyr	Asp	Lys	Trp	Leu	Asn	Ile	Arg	

DOMETO' KASTONOO

					150					133					100
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Gln	Asp	Asn	Trp 180	Ser	Tyr	Tyr	Pro	Leu 185	Leu	Phe	Ser	Gln	Asn 190	Phe	Ala
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Met 225	Glu	Arg	His	Glu	Leu 230	Ser	Gly	Asp	Trp	Lys 235	Lys	Asp	Ser	Arg	Phe 240
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Ala	Val	Asn	Asp 260	Ile	Phe	Gly	Ile	Pro 265	Leu	Leu	Leu	Asn	Phe 270	Met	Val
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Thr	Met 370	Thr	Asp	Leu	Leu	Gln 375	Ile	Ser	Tyr	Lys	Phe 380	Phe	Ala	Leu	Leu
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Glu Pro Tyr Thr Ile Asp Ser Arg Ser Lys Lys Ala Ser Leu Trp Ser
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His Leu Leu Phe Trp Ala Asn Val Ile Asn Leu Ser Val Ile Val Phe
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Gly Glu Ile Leu Tyr Leu Gly Val Ala Tyr Ser Asp Gly Lys Phe Ile
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Asp Ala Val Thr Val Leu Ser Tyr Ile Gly Phe Val Ile Val Gly Met
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                                                          95
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                                                                   336
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Val Lys Glu Leu Glu His Ile Tyr Pro Asn Gly Lys Ala Glu Glu Glu
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atg tat egg ttg gat agg tat etg ega tet tgt tea ega att age att
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Met Tyr Arg Leu Asp Arg Tyr Leu Arg Ser Cys Ser Arg Ile Ser Ile
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                            120
                                                 125
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Thr Tyr Ala Leu Leu Tyr Ser Val Leu Ile Trp Thr Phe Asn Leu Phe
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-			_	ctg Leu 165			_	_							528
			-	tat Tyr			-	-		-					576
		_	-	tcg Ser		_			_	-	-		-	-	624
				gtg Val											672
-				tta Leu	-		-		-	-		-		-	720
				caa Gln 245											768
		-		ttc Phe			_		_			_	-		816
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Ser Ile Met Gln Phe Leu Val Tyr Glu Lys Leu Lys Ile Arg Val 145 150 155 160

Val Gly Gln Thr Leu Pro Tyr Leu Met Tyr Phe Pro Trp Asn Trp His \$165\$ \$170\$

Glu Asn Trp Thr Tyr Tyr Val Leu Leu Phe Cys Gln Asn Phe Ala Gly \$180\$

His Thr Ser Ala Ser Gly Gln Ile Ser Thr Asp Leu Leu Cys Ala \$195\$

Val Ala Thr Gln Val Val Met His Phe Asp Tyr Leu Ala Arg Val Val 210 \$215\$

Glu Lys Gln Val Leu Asp Arg Asp Trp Ser Glu Asn Ser Arg Phe Leu 225 \$230\$ 235 \$240\$

Ala Lys Thr Val Gln Tyr His Gln Arg Ile Leu Arg Leu Met Asp Val \$245\$ \$250\$ \$255

Leu Asn Asp Ile Phe Gly Ile Pro Leu Leu Leu Asn Phe Met Val Ser 260 265 270

Thr Phe Val Ile Cys Phe Val Gly Phe Gln Met Thr Val Gly Val Pro 275 280 285

Pro Asp Ile Met Ile Lys Leu Phe Leu Phe Leu Phe Ser Ser Leu Ser 290 295 300

Gln Val Tyr Leu Ile Cys His Tyr Gly Gln Leu Ile Ala Asp Ala Ser 305 \$310\$ 315 320

Ser Ser Leu Ser Ile Ser Ala Tyr Lys Gln Asn Trp Gln Asn Ala Asp \$325\$ \$330\$ \$335

Ile Arg Tyr Arg Arg Ala Leu Val Phe Phe Ile Ala Arg Pro Gin Arg \$340\$ \$345\$ \$350

Thr Thr Tyr Leu Lys Ala Thr Ile Phe Met Asn Ile Thr Arg Ala Thr \$355\$

Met Thr Asp Leu Leu Gin Val Ser Tyr Lys Phe Phe Ala Leu Leu Arg  $370 \ \ 380$ 

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							acc Thr									240
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ctt Leu	ttc Phe	ggt Gly	cag Gln 180	atc Ile	atg Met	gtg Val	ggc Gly	atg Met 185	acc Thr	ttt Phe	gga Gly	ttc Phe	ggg Gly 190	gga Gly	tca Ser	576
											caa Gln					624
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											gag Glu					720
											ctc Leu					768
											tgt Cys					816
aat Asn	gcg Ala	ttt Phe 275	cac His	aac Asn	gcc Ala	ttg Leu	gtg Val 280	gaa Glu	tgc Cys	att Ile	cgc Arg	ttg Leu 285	cat His	cgc Arg	ttc Phe	864
att Ile	ctg Leu 290	cac His	tgc Cys	tca Ser	cag Gln	gag Glu 295	ttg Leu	gag Glu	aat Asn	cta Leu	ttc Phe 300	agt Ser	cca Pro	tat Tyr	tgt Cys	912
											tgc Cys					960
gtg	ggc	gtt	tcg	ggt	act	cga	gag	gtc	ctg	cgg	att	gtc	aac	cag	cta	1008

Val	Gly	Val	Ser	Gly 325	Thr	Arg	Glu	Val	Leu 330		Ile	Val	Asn	Glr 335	Leu	
cag Gln	tac Tyr	ttg Leu	gga G1y 340	ctg Leu	acc Thr	atc	ttc Phe	gag Glu 345	ctc Leu	cta Leu	atg Met	ttc Phe	acc Thr 350	Tyr	tgt Cys	1056
ggc Gly	gaa Glu	ctc Leu 355	ctc Leu	agt Ser	cgg Arg	cat His	agt Ser 360	att	cga Arg	tct Ser	ggc Gly	gac Asp 365	Ala	ttt Phe	tgg Trp	1104
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Phe	Thr	Lys	Thr	Thr	Leu .	Asp	Val	Leu	Pro	Thr	Gly	Glu	Leu	Gln	Ala	

108

50 55 60

Ile 65	Thr	Asp	Ala	Leu	Thr 70	Met	Thr	Ile	Ile	Tyr 75	Phe	Phe	Thr	Gly	Tyr 80

- Gly Thr Ile Tyr Trp Cys Leu Arg Ser Arg Arg Leu Leu Ala Tyr Met  $85 \hspace{1cm} 90 \hspace{1cm} 95$
- Glu His Met Asn Arg Glu Tyr Arg His His Ser Leu Ala Gly Val Thr \$100\$
- Phe Val Ser Ser His Ala Ala Phe Arg Met Ser Arg Asn Phe Thr Val \$115\$
- Val Trp Ile Met Ser Cys Leu Leu Gly Val Ile Ser Trp Gly Val Ser 130 135 140
- Pro Leu Met Leu Gly Ile Arg Met Leu Pro Leu Gln Cys Trp Tyr Pro 145 150 150 160
- Phe Asp Ala Leu Gly Pro Gly Thr Tyr Thr Ala Val Tyr Ala Thr Gln 165 170 175
- Leu Phe Gly Gln Ile Met Val Gly Met Thr Phe Gly Phe Gly Gly Ser 180 \$180\$
- Leu Phe Val Thr Leu Ser Leu Leu Leu Leu Gly Gln Phe Asp Val Leu 195 200 205
- Tyr Cys Ser Leu Lys Asn Leu Asp Ala His Thr Lys Leu Leu Gly Gly 210 215 220
- Glu Ser Val Asn Gly Leu Ser Ser Leu Gln Glu Glu Leu Leu Gly 225 230 235 240
- Asp Ser Lys Arg Glu Leu Asn Gln Tyr Val Leu Leu Gln Glu His Pro 245 250 255
- Thr Asp Leu Leu Arg Leu Ser Ala Gly Arg Lys Cys Pro Asp Gln Gly 260 265 270
- Asn Ala Phe His Asn Ala Leu Val Glu Cys Ile Arg Leu His Arg Phe 275 280 285
- Ile Leu His Cys Ser Gln Glu Leu Glu Asn Leu Phe Ser Pro Tyr Cys 290 295 300
- Leu Val Lys Ser Leu Gln Ile Thr Phe Gln Leu Cys Leu Leu Val Phe

Val Gly Val Ser Gly Thr Arg Glu Val Leu Arg Ile Val Asn Gln Leu 325 330 335

Gln Tyr Leu Gly Leu Thr Ile Phe Glu Leu Leu Met Phe Thr Tyr Cys \$340\$ \$350\$

Gly Glu Leu Leu Ser Arg His Ser Ile Arg Ser Gly Asp Ala Phe Trp \$355\$ \$360\$ \$365\$

Arg Gly Ala Trp Trp Lys His Ala His Phe Ile Arg Gln Asp Ile Leu  $370 \ \ 380$ 

Ile Phe Leu Val Asn Ser Arg Arg Ala Val His Val Thr Ala Gly Lys 385 390 395 400

Phe Tyr Val Met Asp Val Asn Arg Leu Arg Ser Val Ile Thr Gln Ala 405 410 415

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cgt ccg cag atg ttc cag gag gtg gct cag atg gtg cat ttc cag tgg 96 Arg Pro Gln Met Phe Gln Glu Val Ala Gln Met Val His Phe Gln Trp 20 25 30

cgg aga aat ccg gtg gac aac agc atg gtg aac gca tcc atg gtc ccc 144 Arg Arg Asn Pro Val Asp Asn Ser Met Val Asn Ala Ser Met Val Pro

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		009		- gu	uug	gua	acc	y c c	yay	LLL	guu	aac	gac	LLG	gat	336
Leu	Tyr	Leu	Lys	Arg	Lys	Glu	Ile	Val	Glu	Phe	Val	Asn	Asp	Leu	Asp	
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GIU	Inr	Tyr	Arg	Asn	Phe	Trp	GIn	Arg	Tyr	Arg	Phe	Ile	Arg	Ile	Tyr	
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Ser	His	Leu	Gly	Gly	Pro	Met	Phe	Cys	Val	Val	Pro	Leu	Ala	Leu	Phe	
145					150					155					160	

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ctc	ctt	gga	gga	tgg	ctg	cca	tgc	ggt	gtg	cga	aag	gac	cca	aat	ttc	576
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Tyr	Leu	Leu	Val	Trp	Ser	Phe	Asp	Leu	Met	Cys	Thr	Thr	Cys	Gly	Val	
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Ser	Phe	Phe	Val	Thr	Phe	Asp	Asn	Leu	Phe	Asn	Val	Met	Gln	Gly	His	
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<212> PRT <213> Drosophila melanogaster

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Phe Cys Leu Ser Ala Phe Leu Asn Val Leu Phe Phe Gly Cys Asn Gly 50 55 60

Trp Asp Ile Ile Gly His Phe Trp Leu Gly His Pro Ala Asn Gln Asn 65 70 75 80

Pro Pro Val Leu Ser Ile Thr Ile Tyr Phe Ser Ile Arg Gly Leu Met  $85 \hspace{1cm} 90 \hspace{1cm} 95$ 

Leu Tyr Leu Lys Arg Lys Glu Ile Val Glu Phe Val Asn Asp Leu Asp 100 105 110

Arg Glu Cys Pro Arg Asp Leu Val Ser Gln Leu Asp Met Gln Met Asp  $115 \\ 125 \\ 120 \\ 125$ 

Glu Thr Tyr Arg Asn Phe Trp Gln Arg Tyr Arg Phe Ile Arg Ile Tyr 130 135 140

Ser His Leu Gly Gly Pro Met Phe Cys Val Val Pro Leu Ala Leu Phe 145 150 150 160

Leu Leu Thr His Glu Gly Lys Asp Thr Pro Val Ala Gln His Glu Gln
165 170 175

Leu Leu Gly Gly Trp Leu Pro Cys Gly Val Arg Lys Asp Pro Asn Phe 180 185 190

Tyr Leu Leu Val Trp Ser Phe Asp Leu Met Cys Thr Thr Cys Gly Val

Ser Phe Phe Val Thr Phe Asp Asn Leu Phe Asn Val Met Gln Gly His 210 215 220

Leu Val Met His Leu Gly His Leu Ala Arg Gln Phe Ser Ala Ile Asp 225 230 235 240

Pro Arg Gln Ser Leu Thr Asp Glu Lys Arg Phe Phe Val Asp Leu Arg 245 250 255

Leu Leu Val Gln Arg Gln Gln Leu Leu Asn Gly Leu Cys Arg Lys Tyr 260 265 270

Asn Asp Ile Phe Lys Val Ala Phe Leu Val Ser Asn Phe Val Gly Ala 275 280 285

Gly Ser Leu Cys Phe Tyr Leu Phe Met Leu Ser Glu Thr Ser Asp Val 290 295 300

Leu Ile Ile Ala Gln Tyr Ile Leu Pro Thr Leu Val Leu Val Gly Phe 305 310 315 320

Thr Phe Glu Ile Cys Leu Arg Gly Thr Gln Leu Glu Lys Ala Ser Glu \$325\$ \$330\$

Gly Leu Glu Ser Ser Leu Arg Ser Gln Glu Trp Tyr Leu Gly Ser Arg \$340\$

Arg Tyr Arg Lys Phe Tyr Leu Leu Trp Thr Gln Tyr Cys Gln Arg Thr 355 360 365

Thr Glu Ile Met Gln Leu Ala Tyr Arg Leu Phe Thr Phe Leu Lys Ser 385 390 395 400

His

<210> 57

<211> 1131

<212> DNA

<213> Drosophila melanogaster

<220>

<221> CDS

<222> (1)..(1131)

<223> DOR 92E.1

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ccg Pro	aat Asn	gtg Val	ata Ile 20	agg Arg	cgt Arg	tac Tyr	ctg Leu	cta Leu 25	cgt Arg	ttt Phe	tat Tyr	ctg Leu	gta Val 30	ctc Leu	ggt Gly	96
ttt Phe	ctc Leu	aac Asn 35	ttc Phe	aat Asn	gcc Ala	tat Tyr	gtg Val 40	gtg Val	ggc Gly	gaa Glu	atc Ile	gcg Ala 45	tac Tyr	ttt Phe	ata Ile	144
gtc Val	cat His 50	ata Ile	atg Met	tcg Ser	acg Thr	act Thr 55	act Thr	ctt Leu	ttg Leu	gag Glu	gcc Ala 60	act Thr	gca Ala	gtg Val	gca Ala	192
												cag Gln				240
												gat Asp				288
ata Ile	ttt Phe	cct Pro	tta Leu 100	gat Asp	tta Leu	gaa Glu	gcg Ala	cag Gln 105	cgg Arg	aag Lys	tat Tyr	aac Asn	gta Val 110	tcg Ser	ttt Phe	336
												acc Thr 125				384
												atc Ile				432
												cgc Arg				480
												ctg Leu				528
												gtg Val				576
tcc	tac	gtc	tgc	gtg	gat	ctc	ctg	ctg	atc	gcg	acc	ata	acc	cag	ctg	624

Ser	Tyr	Val 195	Cys	Val	Asp	Leu	Leu 200	Leu	Ile	Ala	Thr	Ile 205	Thr	Gln	Leu	
					ttt Phe											672
					gaa Glu 230											720
gtc Val	tat Tyr	cat His	gcc Ala	agg Arg 245	gcg Ala	ctg Leu	gac Asp	ctc Leu	agc Ser 250	gag Glu	gag Glu	gtc Val	aac Asn	aac Asn 255	ata Ile	768
					ctg Leu											816
					cag Gln											864
					ttt Phe											912
					cgg Arg 310											960
					aaa Lys											1008
					gcc Ala											1056
					atg Met											1104
-	-		-		aca Thr											1131

- <210> 58
- <211> 377
- <212> PRT
- <213> Drosophila melanogaster

## <400> 58

- Met Thr Phe Tyr Lys Thr Ile Gly Glu Asp Leu Tyr Ser Asp Arg Asp 1 5 10 15
- Pro Asn Val Ile Arg Arg Tyr Leu Leu Arg Phe Tyr Leu Val Leu Gly \$20\$ \$25\$ \$30
- Phe Leu Asn Phe Asn Ala Tyr Val Val Gly Glu Ile Ala Tyr Phe Ile  $35 \hspace{1.5cm} 40 \hspace{1.5cm} 45 \hspace{1.5cm}$
- Pro Cys Ile Gly Phe Ser Phe Met Ala Asp Phe Lys Gln Phe Gly Leu  $65 \phantom{000}75\phantom{000}75\phantom{000}80\phantom{000}$
- Thr Val Asn Arg Lys Arg Leu Val Arg Leu Leu Asp Asp Leu Lys Glu 85 90 95
- Ile Phe Pro Leu Asp Leu Glu Ala Gln Arg Lys Tyr Asn Val Ser Phe \$100\$
- Tyr Arg Lys His Met Asn Arg Val Met Thr Leu Phe Thr Ile Leu Cys \$115\$ \$120\$ \$125
- Met Thr Tyr Thr Ser Ser Phe Ser Phe Tyr Pro Ala Ile Lys Ser Thr 130 135 140
- Ile Lys Tyr Tyr Leu Met Gly Ser Glu Ile Phe Glu Arg Asn Tyr Gly 145  $\phantom{\bigg|}$  150  $\phantom{\bigg|}$  155  $\phantom{\bigg|}$  160
- Phe His Ile Leu Phe Pro Tyr Asp Ala Glu Thr Asp Leu Thr Val Tyr \$165\$ \$170\$
- Ser Tyr Val Cys Val Asp Leu Leu Leu Ile Ala Thr Ile Thr Gln Leu 195 200 205
- Thr Met His Phe Asn Phe Ile Ala Asn Asp Leu Glu Ala Tyr Glu Gly 210 215 220

Gly Asp His Thr Asp Glu Glu Asn Ile Lys Tyr Leu His Asn Leu Val 225 230 235 240 Val Tyr His Ala Arg Ala Leu Asp Leu Ser Glu Glu Val Asn Asn Ile 245 250 Phe Ser Phe Leu Ile Leu Trp Asn Phe Ile Ala Ala Ser Leu Val Ile 265 Cys Phe Ala Gly Phe Gln Ile Thr Ala Ser Asn Val Glu Asp Ile Gly 275 280 Val Tyr Phe Ile Phe Phe Ser Ala Ser Leu Val Gln Val Phe Lys Cys 290 295 300 Ser Phe Gln Ser Ser Arg Ile Gly His Ser Ala Phe Asn Gln Asn Trp 305 310 315 320 Leu Pro Cys Ser Thr Lys Tyr Lys Arg Ile Leu Gln Phe Ile Ile Ala 325 330 Arg Ser Gln Lys Pro Ala Ser Ile Arg Pro Pro Thr Phe Pro Pro Ile 345 Ser Phe Asn Thr Phe Met Lys Val Ile Ser Met Ser Tyr Gln Phe Phe 355 360 Ala Leu Leu Arg Thr Thr Tyr Tyr Gly 370 375 <210> 59 <211> 1161 <212> DNA <213> Drosophila melanogaster <220> <221> CDS <222> (1)..(1161) <223> DOR 94D.1 <400> 59 atg gat aaa cac aag gat cgc att gaa too atg cgc cta att ctt cag 48 Met Asp Lys His Lys Asp Arg Ile Glu Ser Met Arg Leu Ile Leu Gln 1 5

Val	Met	Gln	Leu 20	Phe	Gly	Leu	Trp	Pro 25	Trp	Ser	Leu	Lys	Ser 30	Glu	Glu	
							-		-			-		ctg Leu		144
											-		-	gag Glu	-	192
														atg Met		240
														cac His 95		288
														ccg Pro		336
														gag Glu		384
														ttg Leu		432
														tac Tyr		480
														aga Arg 175		528
														acc Thr		576
														ttc Phe		624
atc	tct	ctt	ttg	tac	cga	ctg	ctt	ggt	ctg	cga	ttg	agg	gaa	acg	aag	672

Ile	Ser 210	Leu	Leu	Tyr	Arg	Leu 215	Leu	Gly	Leu	Arg	Leu 220	Arg	Glu	Thr	Lys	
	atg Met															720
	atg Met															768
	tct Ser															816
	ttt Phe															864
	cag Gln 290															912
	tac Tyr															960
	ctg Leu															1008
	att Ile														ccg Pro	1056
								Phe					Pro		ttt Phe	1104
		Thr					Tyr					Leu			aat Asn	1152
-	tcg Ser															1161

<210> 60

<211> 387

<212> PRT

<213> Drosophila melanogaster

<400> 60

Met Asp Lys His Lys Asp Arg Ile Glu Ser Met Arg Leu Ile Leu Gln  $1 \hspace{1cm} 5 \hspace{1cm} 10 \hspace{1cm} 15$ 

Val Met Gln Leu Phe Gly Leu Trp Pro Trp Ser Leu Lys Ser Glu Glu \$20\$

Glu Trp Thr Phe Thr Gly Phe Val Lys Arg Asn Tyr Arg Phe Leu Leu  $35 \hspace{1.5cm} 40 \hspace{1.5cm} 45$ 

His Leu Pro Ile Thr Phe Thr Phe Ile Gly Leu Met Trp Leu Glu Ala  $50 \ \ 55 \ \ 60$ 

Phe Ile Ser Ser Asn Leu Glu Gln Ala Gly Gln Val Leu Tyr Met Ser 65 70 75 80

Ile Thr Glu Met Ala Leu Val'Val Lys Ile Leu Ser Ile Trp His Tyr  $85 \hspace{1cm} 90 \hspace{1cm} 95$ 

Arg Thr Glu Ala Trp Arg Leu Met Tyr Glu Leu Gln His Ala Pro Asp \$100\$

Tyr Gln Leu His Asn Gln Glu Glu Val Asp Phe Trp Arg Arg Glu Gln \$115\$ \$120\$ \$125\$

Arg Phe Phe Lys Trp Phe Phe Tyr Ile Tyr Ile Leu Ile Ser Leu Gly 130 135 140

Val Val Tyr Ser Gly Cys Thr Gly Val Leu Phe Leu Glu Gly Tyr Glu 145 \$150\$

Leu Pro Phe Ala Tyr Tyr Val Pro Phe Glu Trp Gln Asn Glu Arg Arg 165 \$170\$

Tyr Trp Phe Ala Tyr Gly Tyr Asp Met Ala Gly Met Thr Leu Thr Cys \$180\$ \$190\$

Ile Ser Asn Ile Thr Leu Asp Thr Leu Gly Cys Tyr Phe Leu Phe His

Ile Ser Leu Leu Tyr Arg Leu Leu Gly Leu Arg Leu Arg Glu Thr Lys 210 220

Asn Met Lys Asn Asp Thr Ile Phe Gly Gln Gln Leu Arg Ala Ile Phe 230 235 225

Ile Met His Gln Arg Ile Arg Ser Leu Thr Leu Thr Cys Gln Arg Ile 245 250

Val Ser Pro Tyr Ile Leu Ser Gln Ile Ile Leu Ser Ala Leu Ile Ile 265 260

Cys Phe Ser Gly Tyr Arg Leu Gln His Val Gly Ile Arg Asp Asn Pro 280

Gly Gln Phe Ile Ser Met Leu Gln Phe Val Ser Val Met Ile Leu Gln 295

Ile Tyr Leu Pro Cys Tyr Tyr Gly Asn Glu Ile Thr Val Tyr Ala Asn 315 320 305 310

Gln Leu Thr Asn Glu Val Tyr His Thr Asn Trp Leu Glu Cys Arg Pro 330 325

Pro Ile Arg Lys Leu Leu Asn Ala Tyr Met Glu His Leu Lys Lys Pro 345 350 340

Val Thr Ile Arg Ala Gly Asn Tyr Phe Ala Val Gly Leu Pro Ile Phe 360 355

Val Lys Thr Ile Asn Asn Ala Tyr Ser Phe Leu Ala Leu Leu Leu Asn 375

Val Ser Asn 385

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<211> 1101

<212> DNA

<213> Drosophila melanogaster

<220>

<221> CDS

<222> (1)..(1101)

<400> 61

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	cgt Arg															96
gta Val	tta Leu	acc Thr 35	tgg Trp	cta Leu	aaa Lys	cga Arg	ata Ile 40	tat Tyr	cct Pro	ttt Phe	gta Val	ctg Leu 45	cac His	ctt Leu	cca Pro	144
ctg Leu	acc Thr 50	ttc Phe	acg Thr	tat Tyr	att Ile	gcc Ala 55	tta Leu	atg Met	tgg Trp	tat Tyr	gaa Glu 60	gct Ala	att Ile	aca Thr	tcg Ser	192
tca Ser 65	gat Asp	ttt Phe	gag Glu	gaa Glu	gct Ala 70	ggt Gly	caa Gln	gtt Val	ctg Leu	tac Tyr 75	atg Met	tcc Ser	atc Ile	acc Thr	gaa Glu 80	240
ctg Leu	gca Ala	ttg Leu	gtc Val	act Thr 85	aaa Lys	ctg Leu	ctg Leu	aat Asn	att Ile 90	tgg Trp	tat Tyr	cgt Arg	cgt Arg	cat His 95	gaa Glu	288
gct Ala	gct Ala	agt Ser	cta Leu 100	atc Ile	cac His	gaa Glu	ttg Leu	caa Gln 105	cac His	gat Asp	ccc Pro	gca Ala	ttt Phe 110	aat Asn	ctg Leu	336
cgc Arg	aat Asn	tcg Ser 115	gag Glu	gaa Glu	atc Ile	aaa Lys	ttc Phe 120	tgg Trp	çag Gln	caa Gln	aat Asn	cag Gln 125	agg Arg	aac Asn	ttt Phe	384
aag Lys	aga Arg 130	Ile	ttt Phe	tac Tyr	tgg Trp	tac Tyr 135	atc	tgg Trp	ggc Gly	agc Ser	ctt Leu 140	Phe	gtg Val	gct Ala	gta Val	432
atg Met 145	ggt Gly	tat Tyr	ata Ile	agc Ser	gtg Val 150	Phe	ttc Phe	cag Gln	gaç	gat Asp 155	Туг	gag Glu	ctg Leu	ccc Pro	Phe 160	480
Gl)	tac Tyr	tac Tyr	gtg Val	cca Pro	Phe	gaç Glu	tgg Trp	cgc Arg	200 Th:	Arg	g gaa g Glu	a cga ı Arç	tac Tyr	Phe 175	tac Tyr	528
gct Ala	tgq a Trp	g ggc	tat 7 Ty: 180	: Asr	gtg Val	gto Val	g gco	ato Met 185	Thi	c cto	g tgo	tgt GCys	cta Lev	ı Sei	aac Asn	576
ato Ile	cta E Lev	Let	ı Ası	aca Thi	a cta r Leu	ı Gl	у Су:	tat s Tyr	Ph	c ato	g tto	c cade His	s Ile	c gco e Ala	tcg a Ser	624

				ttg Leu												672
				aga Arg												720
				ttg Leu 245												768
				gtg Val												816
tat Tyr	cga Arg	ctg Leu 275	gtg Val	cac His	atg Met	ggc Gly	ttc Phe 280	aag Lys	cag Gln	cga Arg	cct Pro	gga Gly 285	ctc Leu	ttc Phe	gtg Val	864
				ttc Phe												912
tgt Cys 305	tac Tyr	tac Tyr	ggc Gly	aat Asn	gag Glu 310	ttg Leu	acc Thr	ttt Phe	cat	gcc Ala 315	Asn	gca Ala	ctc Leu	act Thr	aat Asn 320	960
				acc Thr 325						Ser						1008
ctg Leu	ctt Leu	aac	tgc Cys 340	Tyr	atg Met	gag Glu	ttc Phe	ctc Leu 345	Lys	cga Arg	ccg Pro	gtt Val	aaa Lys 350	Thr	atc Ile	1056
aac Asn	aat Asn	geo Ala	туг	agt Ser	tto Phe	tto Phe	gcc Ala	Leu	ctç Lev	cta Leu	aag Lys	ata Ile 365	Ser	aaq Lys		1101

<210> 62 <211> 367

<212> PRT <213> Drosophila melanogaster

<400> 62

Met 1	Glu	Ser	Thr	Asn 5	Arg	Leu	Ser	Ala	Ile 10	Gln	Thr	Leu	Leu	Val 15	Ile
Gln	Arg	Trp	11e 20	Gly	Leu	Leu	Lys	Trp 25	Glu	Asn	Glu	Gly	Glu 30	Asp	Gly
Val	Leu	Thr 35	Trp	Leu	Lys	Arg	Ile 40	Tyr	Pro	Phe	Val	Leu 45	His	Leu	Pro
Leu	Thr 50	Phe	Thr	Tyr	Ile	Ala 55	Leu	Met	Trp	Tyr	Glu 60	Ala	Ile	Thr	Ser
Ser 65	Asp	Phe	Glu	Glu	Ala 70	Gly	Gln	Val	Leu	Tyr 75	Met	Ser	Ile	Thr	Glu 80
Leu	Ala	Leu	Val	Thr 85	Lys	Leu	Leu	Asn	Ile 90	Trp	Tyr	Arg	Arg	His 95	Glu
Ala	Ala	Ser	Leu 100		His	Glu	Leu	Gln 105	His	Asp	Pro	Ala	Phe 110	Asn	Leu
Arg	Asn	Ser		Glu	Ile	Lys	Phe 120	Trp	Gln	Gln	Asn	Gln 125	Arg	Asn	Phe
Lys	Arg		Phe	Tyr	Trp	Tyr 135		Trp	Gly	Ser	Leu 140	Phe	Val	Ala	Val
Met 145	-	Tyr	Ile	Ser	Val 150		Phe	Gln	. Glu	Asp 155		Glu	Leu	Pro	Phe 160
Gly	туг	Туг	. Val	Pro 165		Glu	Trp	Arg	Thr 170		Glu	Arg	Tyr	Phe 175	Tyr
Ala	Trp	Gly	7 Ty:		ı Val	. Val	. Alā	Met 185		Lev	ı Cys	Cys	190	Ser	Asn
Ιlє	e Le	1 Le		, Thi	r Lev	ı Gly	200 200		: Phe	e Met	: Phe	205	Ile	Ala	Ser
Let	ı Ph	e Ar	g Le	a Let	ı Gly	Met	Are	j Let	ı Glı	ı Ala	a Let	Lys	s Asr	Ala	Ala

Leu Phe Arg Leu Leu Gly Met Arg Leu Glu Ala Leu Lys Asn Ala Al 210 215 220

Glu Glu Lys Ala Arg Pro Glu Leu Arg Arg Ile Phe Gln Leu His Thr 225 230 235

Lys Val Arg Arg Leu Thr Arg Glu Cys Glu Val Leu Val Ser Pro Tyr \$245\$

	Gln Val 260	Val Phe	Ser Ala 265	Phe Ile	Ile Cys	Phe Ser 270	Ala
Tyr Arg Leu 275	Val His	Met Gly	Phe Lys 280	Gln Arg	Pro Gly 285	Leu Phe	Val
Thr Thr Val 290	Gln Phe	Val Ala 295	Val Met	Ile Val	Gln Ile 300	Phe Leu	Pro
Cys Tyr Tyr 305	Gly Asn	Glu Leu 310	Thr Phe	His Ala 315	Asn Ala	Leu Thr	Asn 320
Ser Val Phe	325			330		335	
Leu Leu Asn	340		345			350	
Asn Asn Ala 355	Tyr Ser	rne rne	360	Leu Leu	365	ser Lys	
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<212> DNA <213> Droso	phila mel	Lanogast	er				
<212> DNA	(1095)	Lanogaste	er				
<212> DNA <213> Droso <220> <221> CDS <222> (1)	(1095) 1.1			aag gag	gga gtc	ctg cgc	: tac 48
<212> DNA <213> Droso <220> <221> CDS <222> (1) <223> DORLU <400> 63	(1095) 1.1 atc gga	tgg att	ccg ccg				Tyr
<pre>&lt;212&gt; DNA &lt;213&gt; Droso &lt;220&gt; &lt;221&gt; CDS &lt;222&gt; (1) &lt;223&gt; DORLU &lt;400&gt; 63 atg tgg ctc Met Trp Leu</pre>	(1095) 1.1  atc gga Ile Gly 5	tgg att Trp Ile	ccg ccg Pro Pro	Lys Glu 10 ttc gcc Phe Ala	Gly Val	Leu Arg 15 gtg ttt	Tyr
<212> DNA <213> Droso <220> <221> CDS <222> (1) <223> DORLU <400> 63 adg tgg ctc Met Trp Leu  1 gtg tat ctc	(1095) 1.1 atc gga Ile Gly 5 ttc tgg Phe Trp 20 ggc ttc Gly Phe	tgg att Trp Ile acc tgc Thr Cys	ccg ccg Pro Pro gtg ccc Val Pro 25	Lys Glu 10 ttc gcc Phe Ala	ttc ggg Phe Gly	Leu Arg 15 gtg ttt Val Phe 30 aag aag	tac 96

50 55 60

										ctc Leu			240
-	_	-			_	-	_	-	-	agg Arg	-		288
-	-	-	-	 			_			cgc Arg	-		336
										gcg Ala 125			384
										tcc Ser			432
										tgg Trp			480
										cag Gln			528
										cgg Arg			576
										gat Asp 205			624
										gtg Val			672
										atg Met			720
										ttg Leu			768

Here are a supplied to the

_								aac Asn 265						-	-	816
	_		-				_	ctg Leu				_		-		864
								gcc Ala								912
								gag Glu								960
								cag Gln								1008
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		_			-			aca Thr								1095
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	0> 6 Trp		Ile	Gly 5	Trp	Ile	Pro	Pro	Lys 10	Glu	Gly	Val	Leu	Arg 15	Tyr	
Val	Tyr	Leu	Phe 20	Trp	Thr	Cys	Val	Pro 25	Phe	Ala	Phe	Gly	Val 30	Phe	Tyr	
Leu	Pro	Val 35	Gly	Phe	Ile	Ile	Ser 40	Tyr	Val	Gln	Glu	Phe 45	Lys	Asn	Phe	
Thr	Pro 50	_	Glu	Phe	Leu	Thr	Ser	Leu	Gln	Val	Cys 60	Ile	Asn	Val	Tyr	

the minimum of contribution or

- Gly Ala Ser Val Lys Ser Thr Ile Thr Tyr Leu Phe Leu Trp Arg Leu 65 70 75 80
- Arg Lys Thr Glu Ile Leu Leu Asp Ser Leu Asp Lys Arg Leu Ala Asn 85 90 95
- Asp Ser Asp Arg Glu Arg Ile His Asn Met Val Ala Arg Cys Asn Tyr \$100\$ \$100\$
- Ala Phe Leu Ile Tyr Ser Phe Ile Tyr Cys Gly Tyr Ala Gly Ser Thr \$115\$
- Phe Leu Ser Tyr Ala Leu Ser Gly Arg Pro Pro Trp Ser Val Tyr Asn 130 135 140
- Pro Phe Ile Asp Trp Arg Asp Gly Met Gly Ser Leu Trp Ile Gln Ala 145  $\phantom{\bigg|}150\phantom{\bigg|}150\phantom{\bigg|}155\phantom{\bigg|}$
- Ile Phe Glu Tyr Ile Thr Met Ser Phe Ala Val Leu Gln Asp Gln Leu 165 170 175
- Ser Asp Thr Tyr Pro Leu Met Phe Thr Ile Met Phe Arg Ala His Met 180 185 190
- Glu Val Leu Lys Asp His Val Arg Ser Leu Arg Met Asp Pro Glu Arg 195 200 205
- Ser Glu Ala Asp Asn Tyr Gln Asp Leu Val Asn Cys Val Leu Asp His 210 215 220
- Lys Thr Ile Leu Lys Cys Cys Asp Met Ile Arg Pro Met Ile Ser Arg 225 230 235
- Thr Ile Phe Val Gln Phe Ala Leu Ile Gly Ser Val Leu Gly Leu Thr 245 250 255
- Leu Val Asn Val Phe Phe Phe Ser Asn Phe Trp Lys Gly Val Ala Ser 260 265 270
- Leu Leu Phe Val Ile Thr Ile Leu Leu Gln Thr Phe Pro Phe Cys Tyr \$275\$
- Thr Cys Asn Met Leu Ile Asp Asp Ala Gln Asp Leu Ser Asn Glu Ile 290 295 300
- Phe Gln Ser Asn Trp Val Asp Ala Glu Pro Arg Tyr Lys Ala Thr Leu 305 310 315 320

palitically seminance condition

Val Leu Phe Met His His Val Gln Gln Pro Ile Ile Phe Ile Ala Gly 325 330 335	
Gly Ile Phe Pro Ile Ser Met Asn Ser Asn Ile Thr Val Arg Ile Thr $340 \\ \hspace{1.5cm} 345 \\ \hspace{1.5cm} 350 \\ \hspace{1.5cm}$	
Ser Phe Leu Pro Thr Ala Tyr Phe Thr Phe Asp Pro Phe 355 360 365	
<210> 65	
<211> 1233	
<212> DNA <213> Drosophila melanogaster	
<220>	
<221> CDS	
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Met Thr Lys Phe Phe Phe Lys Arg Leu Gln Thr Ala Pro Leu Asp Gln  1 5 10 15	
	0.5
gag gtg agt tcc ctt gat gcc agc gac tac tac tac cgc atc gca ttt Glu Val Ser Ser Leu Asp Ala Ser Asp Tyr Tyr Tyr Arg Ile Ala Phe	96
20 25 30	
ttc ctg ggc tgg acc ccg ccc aag ggg gct ctg ctc cga tgg atc tac	144
Phe Leu Gly Trp Thr Pro Pro Lys Gly Ala Leu Leu Arg Trp Ile Tyr 35 40 45	
tee etq tqq act etq ace acq atq tqq etq qqt ate qtq tae etq ecq	192
Ser Leu Trp Thr Leu Thr Thr Met Trp Leu Gly Ile Val Tyr Leu Pro	
50 55 60	
ctc gga ctg agc ctc acc tat gtg aag cac ttc gat aga ttc acg ccg Leu Gly Leu Ser Leu Thr Tyr Val Lys His Phe Asp Arg Phe Thr Pro	240
65 70 75 80	
acq gag tto ctg acc tcc ctg cag gtg gat atc aac tgc atc ggg aac	288
Thr Glu Phe Leu Thr Ser Leu Gln Val Asp Ile Asn Cys Ile Gly Asn	
85 90 95	
gtg atc aag toa tgc gta act tat too cag atg tgg cgt ttt cgc cgg	336

Val	Ile	Lys	Ser 100	Cys	Val	Thr	Tyr	Ser 105	Gln	Met	Trp	Arg	Phe 110	Arg	Arg	
		gag Glu 115								-	-			-		384
		cga Arg														432
		ttc Phe														480
	_	gtt Val		-			-			_	_				_	528
	-	tgg Trp						_				-			_	576
		tgt Cys 195		_					-	_		_	_		_	624
		gcc Ala						-			-		_			672
		gat Asp														720
_	-	cac His														768
		cag Gln	-		-			-			_	_				816
	-	cag Gln 275		_	_	-			-	_		_		-		864
age	atc	ctc	ttc	ttt	сса	aac	acc	att	taa	acq	atc	ato	gca	aac	ata	912

Ser	Ile 290	Leu	Phe	Phe	Pro	Asn 295	Thr	Ile	Trp	Thr	Ile 300	Met	Ala	Asn	Val	
tcg Ser 305	ttc Phe	atc Ile	gtg Val	gcc Ala	atc Ile 310	tgt Cys	aca Thr	gag Glu	tcc Ser	ttt Phe 315	cca Pro	tgc Cys	tgc Cys	atg Met	ctc Leu 320	960
					gag Glu											1008
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					aat Asn											1233
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	)> 66 Thr		Phe	Phe 5	Phe	Lys	Arg	Leu	Gln 10	Thr	Ala	Pro	Leu	Asp 15	Gln	
Glu	Val	Ser	Ser 20	Leu	Asp	Ala	Ser	Asp 25	Tyr	Tyr	Tyr	Arg	Ile 30	Ala	Phe	
Phe	Leu	Gly 35	Trp	Thr	Pro	Pro	Lys 40	Gly	Ala	Leu	Leu	Arg 45	Trp	Ile	Tyr	
Ser	Leu	Trp	Thr	Leu	Thr	Thr	Met	Trp	Leu	Gly	Ile	Val	Tyr	Leu	Pro	

50 55 60

Leu Gly Leu Ser Leu Thr Tyr Val Lys His Phe Asp Arg Phe Thr Pro 65 70 75 80

- Thr Glu Phe Leu Thr Ser Leu Gln Val Asp Ile Asn Cys Ile Gly Asn 85 90 95
- Val Ile Lys Ser Cys Val Thr Tyr Ser Gln Met Trp Arg Phe Arg Arg  $100 \\ 105 \\ 110$
- Met Asn Glu Leu Ile Ser Ser Leu Asp Lys Arg Cys Val Thr Thr Thr 115 120 125
- Gln Arg Arg Ile Phe His Lys Met Val Ala Arg Val Asn Leu Ile Val 130 135 140
- Ile Leu Phe Leu Ser Thr Tyr Leu Gly Phe Cys Phe Leu Thr Leu Phe 145 \$150\$
- Thr Ser Val Phe Ala Gly Lys Ala Pro Trp Gln Leu Tyr Asn Pro Leu 165 170 170
- Val Asp Trp Arg Lys Gly His Trp Gln Leu Trp Ile Ala Ser Ile Leu 180 185 190
- Glu Tyr Cys Val Val Ser Ile Gly Thr Met Gln Glu Leu Met Ser Asp \$195\$ \$200\$ \$205\$
- Thr Tyr Ala Ile Val Phe Ile Ser Leu Phe Arg Cys His Leu Ala Ile 210 \$215\$
- Leu Arg Asp Arg Ile Ala Asn Leu Arg Gln Asp Pro Lys Leu Ser Glu 225 230 235
- Met Glu His Tyr Glu Gln Met Val Ala Cys Ile Gln Asp His Arg Thr \$245\$
- Ile Ile Gln Cys Ser Gln Ile Ile Arg Pro Ile Leu Ser Ile Thr Ile  $260 \hspace{1.5cm} 265 \hspace{1.5cm} 270 \hspace{1.5cm}$
- Phe Ala Gln Phe Met Leu Val Gly Ile Asp Leu Gly Leu Ala Ala Ile 275 280 285
- Ser Ile Leu Phe Phe Pro Asn Thr Ile Trp Thr Ile Met Ala Asn Val  $290 \ \ 295 \ \ 300$
- Ser Phe Ile Val Ala Ile Cys Thr Glu Ser Phe Pro Cys Cys Met Leu

Cys	Glu	His	Leu	Ile	G1u	Asp	Ser	Va1	His	Val	Ser	Asn	Ala	Leu	Phe
				325					330					335	

His Ser Asn Trp Ile Thr Ala Asp Arg Ser Tyr Lys Ser Ala Val Leu \$340\$ \$345\$

Tyr Phe Leu His Arg Ala Gln Gln Pro Ile Gln Phe Thr Ala Gly Ser \$355\$

Ile Phe Pro Ile Ser Val Gln Ser Asn Ile Ala Val Ala Lys Phe Ala 370 380

Phe Thr Ile Ile Thr Ile Val Asn Gln Met Asn Leu Gly Glu Lys Phe 385 390 395 400

Phe Ser Asp Arg Ser Asn Gly Asp Ile Asn Pro \$405\$

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<213> Drosophila melanogaster

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<223> DORLU 4.1

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toc ogg gat tog otg atc tac tta aac aga toc ata gat caa atg gga 96 Ser Arg Asp Ser Leu Ile Tyr Leu Asn Arg Ser Ile Asp Gln Met Gly 20 25 30

tgg aga ctg ccg cca cga act aag ccg tac tgg tgg ctc tat tac att  $\,$  144 Trp Arg Leu Pro Pro Arg Thr Lys Pro Tyr Trp Trp Leu Tyr Tyr Ile  $\,$  35  $\,$  40  $\,$  45

tgg aca ttg gtg gtc ata gta ctc gtc ttt atc ttt ata ccc tat gga  $^{\circ}$  192 Trp Thr Leu Val Val Ileu Val Leu Val Phe Ile Phe Ile Pro Tyr Gly  $^{\circ}$  50  $^{\circ}$  55  $^{\circ}$  60  $^{\circ}$ 

			ata Ile 70									240
			cag Gln									288
			ttg Leu									336
		-	atg Met	-	-	-		-	_	 		384
			gca Ala									432
			ttc Phe 150									480
			act Thr									528
			tat Tyr									576
-		_	gcc Ala			_	-	-				624
Tyr			cgg Arg									672
			gat Asp 230	-			-	-			-	720
			gta Val									768

						ata Ile										816
						ggt Gly										864
						gtt Val 295										912
						ttt Phe										960
						aac Asn										1008
						acc Thr										1056
						act Thr								-		1104
						gcc Ala 375										1152
						gcc Ala										1191
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Trp	Arg	Leu 35	Pro	Pro	Arg	Thr	Lys 40	Pro	Tyr	Trp	Trp	Leu 45	Tyr	Tyr	Ile
Ten	Th s	7	77-7	77-7	T1.	**- 3	Ŧ.		ъ.				_	_	

Trp Thr Leu Val Val Ile Val Leu Val Phe Ile Phe Ile Pro Tyr Gly
50 60

Leu Ile Met Thr Gly Ile Lys Glu Phe Lys Asn Phe Thr Thr Thr Asp 65 70 75 80

Leu Phe Thr Tyr Val Gln Val Pro Val Asn Thr Asn Ala Ser Ile Met \$85\$ 90 95

Lys Gly Ile Ile Val Leu Phe Met Arg Arg Arg Phe Ser Arg Ala Gln \$100\$

Lys Met Met Asp Ala Met Asp Ile Arg Cys Thr Lys Met Glu Glu Lys \$115\$ \$120\$

Val Gln Val His Arg Ala Ala Ala Leu Cys Asn Arg Val Val Val Ile 130 \$135\$

Tyr His Cys Ile Tyr Phe Gly Tyr Leu Ser Met Ala Leu Thr Gly Ala 145 \$150\$

Leu Val Ile Gly Lys Thr Pro Phe Cys Leu Tyr Asn Pro Leu Val Asn 165 170 175

Pro Asp Asp His Phe Tyr Leu Ala Thr Ala Ile Glu Ser Val Thr Met 180 185 190

Ala Gly Ile Ile Leu Ala Asn Leu Ile Leu Asp Val Tyr Pro Ile Ile 195 \$200\$

Tyr Val Val Val Leu Arg Ile His Met Glu Leu Leu Ser Glu Arg Ile 210 215 220

Lys Thr Leu Arg Thr Asp Val Glu Lys Gly Asp Asp Gln His Tyr Ala 225 \$230\$ 235 \$240

Glu Leu Val Glu Cys Val Lys Asp His Lys Leu Ile Val Glu Tyr Gly  $245 \hspace{1.5cm} 250 \hspace{1.5cm} 255$ 

Asn Thr Leu Arg Pro Met Ile Ser Ala Thr Met Phe Ile Gln Leu Leu 260 265 270

Ser Val Gly Leu Leu Gly Leu Ala Ala Val Ser Met Gln Phe Tyr

275	280	285

Asn Thr Val Met Glu Arg Val Val Ser Gly Val Tyr Thr Ile Ala Ile  $290 \hspace{1.5cm} 295 \hspace{1.5cm} 300 \hspace{1.5cm}$ 

Leu Ser Gln Thr Phe Pro Phe Cys Tyr Val Cys Glu Gln Leu Ser Ser 305 310 315

Asp Cys Glu Ser Leu Thr Asn Thr Leu Phe His Ser Lys Trp Ile Gly \$325\$

Ala Glu Arg Arg Tyr Arg Thr Thr Met Leu Tyr Phe Ile His Asn Val \$340\$ \$350\$

Gln Gln Ser Ile Leu Phe Thr Ala Gly Gly Ile Phe Pro Ile Cys Leu \$355\$

Asn Thr Asn Ile Lys Met Ala Lys Phe Ala Phe Ser Val Val Thr Ile  $370 \ \ 375 \ \ \ 380$ 

Val Asn Glu Met Asp Leu Ala Glu Lys Leu Arg Arg Glu 385 390 395

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<223> DORLU 5.1

<400> 69

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tot cog gae toa tit aga tae tit gag tat gga atg tit tge atg gga 9. Ser Pro Asp Ser Phe Arg Tyr Phe Glu Tyr Gly Met Phe Cys Met Gly 20 25 30

tgg cac aca cca gca acg cat aag ata atc tac tat ata aca tcc tgt  $\,$  144 Trp His Thr Pro Ala Thr His Lys Ile Ile Tyr Tyr Ile Thr Ser Cys  $\,$  35  $\,$  40  $\,$  45

				tgt Cys								192
				att Ile 70								240
				ttc Phe								288
				att Ile								336
				cgt Arg								384
			-	cgt Arg	-	-	-				_	432
				act Thr 150								480
				cgc Arg								528
				tgg Trp								576
				caa Gln								624
				aga Arg								672
 -	-	-	Thr	gat Asp			Ser	-	-	-		720

					atc Ile									768
					gcg Ala									816
					ctt Leu									864
					gga Gly									912
					cca Pro 310									960
					gtg Val									1008
					aag Lys			-	-		_	_		1056
-				-	ttt Phe		-							1104
					gtg Val		_	_	-	-		-		1152
					ata Ile 390									1191
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<400> 70

Met Leu Phe Asn Tyr Leu Arg Lys Pro Asn Pro Thr Asn Leu Leu Thr

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Ser	Pro	Asp	Ser 20	Phe	Arg	Tyr	Phe	G1u 25	Tyr	Gly	Met	Phe	Cys 30	Met	Gly
Trp	His	Thr 35	Pro	Ala	Thr	His	Lys 40	Ile	Ile	Tyr	Tyr	Ile 45	Thr	Ser	Cys
Leu	Ile 50	Phe	Ala	Trp	Cys	Ala 55	Val	Tyr	Leu	Pro	Ile 60	Gly	Ile	Ile	Ile
Ser 65	Phe	Lys	Thr	Asp	Ile 70	Asn	Thr	Phe	Thr	Pro 75	Asn	Glu	Leu	Leu	Thr 80
Val	Met	Gln	Leu	Phe 85	Phe	Asn	Ser	Val	Gly 90	Met	Pro	Phe	Lys	Val 95	Leu
Phe	Phe	Asn	Leu 100	Tyr	Ile	Ser	Gly	Phe 105	Tyr	Lys	Ala	Lys	Lys 110	Leu	Leu
Ser	Glu	Met 115	Asp	Lys	Arg	Cys	Thr 120	Thr	Leu	Lys	Glu	Arg 125	Val	Glu	Val
His	Gln 130	Gly	Val	Val	Arg	Cys 135	Asn	Lys	Ala	Tyr	Leu 140	Ile	Tyr	Gln	Phe
Ile 145	Tyr	Thr	Ala	Tyr	Thr 150	Ile	Ser	Thr	Phe	Leu 155	Ser	Ala	Ala	Leu	Ser 160
Gly	Lys	Leu	Pro	Trp 165	Arg	Ile	Tyr	Asn	Pro 170	Phe	Val	Asp	Phe	Arg 175	Glu
Ser	Arg	Ser	Ser 180	Phe	Trp	Lys	Ala	Ala 185	Leu	Asn	Glu	Thr	Ala 190	Leu	Met
Leu	Phe	Ala 195	Val	Thr	Gln	Thr	Leu 200	Met	Ser	Asp	Ile	Tyr 205	Pro	Leu	Leu
Tyr	Gly 210	Leu	Ile	Leu	Arg	Val 215	His	Leu	Lys	Leu	Leu 220	Arg	Leu	Arg	Val

Glu Ser Leu Cys Thr Asp Ser Gly Lys Ser Asp Ala Glu Asn Glu Gln 225 230 230 235

Asp Leu Ile Lys Cys Ile Lys Asp His Asn Leu Ile Ile Asp Tyr Ala \$245\$ \$250\$

Ala Ala Ile Arg Pro Ala Val Thr Arg Thr Ile Phe Val Gln Phe Leu

	260	2	265	270	
Leu Ile Gly 275	Ile Cys Leu	Gly Leu S 280	Ser Met Ile A	Asn Leu Leu P 285	he Phe
Ala Asp Ile 290	Trp Thr Gly	Leu Ala T 295		Tyr Ile Asn G 300	ly Leu
Met Val Gln 305	Thr Phe Pro	Phe Cys P	he Val Cys A	Asp Leu Leu L	ys Lys 320
Asp Cys Glu	Leu Leu Val 325	Ser Ala I	le Phe His S	Ser Asn Trp I 3	le Asn
Ser Ser Arg	Ser Tyr Lys 340		eu Arg Tyr E 345	Phe Leu Lys A 350	sn Ala
Gln Lys Ser 355	Ile Ala Phe	Thr Ala G 360	Sly Ser Ile E	Phe Pro Ile S 365	er Thr
Gly Ser Asn 370	Ile Lys Val	Ala Lys L 375		Ser Val Val T 880	hr Phe
Val Asn Gln 385	Leu Asn Ile 390	Ala Asp A	arg Leu Thr I 395	Lys Asn	
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cag gca ccg gat ggc agt cga ccg acc acg agc agc aca tgg caa cgc

20

cgg cga gcg ttt agg aat ctc ttc aat tgc ttc tat gcc ctt ggc atg Arg Arg Ala Phe Arg Asn Leu Phe Asn Cys Phe Tyr Ala Leu Gly Met

Gln	Ala	Pro 35	Asp	Gly	Ser	Arg	Pro 40	Thr	Thr	Ser	Ser	Thr 45	Trp	Gln	Arg	
											tgg Trp 60					192
											atg Met					240
											atc Ile					288
											ttg Leu					336
											cgg Arg					384
											ttt Phe 140					432
											tcc Ser					480
								_			gcc Ala			_		528
					-			_	_		tgc Cys		_	-		576
											cac His					624
-			-	-			_			-	cgg Arg 220					672
ttg	ctg	gcc	agg	cgg	gtg	gag	aag	ctg	ggc	acg	gat	gat	agt	ggc	cag	720

Leu 225	. Leu	Ala	Arg	Arg	Val 230	Glu	Lys	Leu	Gly	Thr 235		Asp	Ser	Gly	Gln 240	
gtg Val	gag Glu	ato	tat Tyr	Pro 245	gat Asp	gag Glu	cgg Arg	cgg Arg	cag Gln 250	gag Glu	gag Glu	cat	tgc Cys	gcg Ala 255	gaa Glu	768
ctg Leu	cag Gln	cgc Arg	tgc Cys 260	Ile	gta Val	gat Asp	cac	cag Gln 265	acg Thr	atg Met	ctg Leu	cag Gln	ctg Leu 270	ctc Leu	gac Asp	816
tgc Cys	att Ile	agt Ser 275	ccc Pro	gtc Val	atc Ile	tcg Ser	cgt Arg 280	acc Thr	ata Ile	ttc Phe	gtt Val	cag Gln 285	ttc Phe	ctg Leu	atc Ile	864
					ggc Gly											912
aat Asn 305	acg Thr	aac Asn	acg Thr	aag Lys	atc Ile 310	gca Ala	tcg Ser	atc Ile	att Ile	tac Tyr 315	ctg Leu	ctg Leu	gcg Ala	gtg Val	acc Thr 320	960
					tgt Cys											1008
					ctg Leu											1056
					aag Lys											1104
					acc Thr											1152
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					ggc Gly											1239

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<213> Drosophila melanogaster
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Gln Ala Pro Asp Gly Ser Arg Pro Thr Thr Ser Ser Thr Trp Gln Arg
         35
                             40
Ile Tyr Ala Cys Phe Ser Val Val Met Tyr Val Trp Gln Leu Leu Leu
     50
Val Pro Thr Phe Phe Val Ile Ser Tyr Arg Tyr Met Gly Gly Met Glu
                     70
Ile Thr Gln Val Leu Thr Ser Ala Gln Val Ala Ile Asp Ala Val Ile
                                     90
Leu Pro Ala Lys Ile Val Ala Leu Ala Trp Asn Leu Pro Leu Leu Arg
Arg Ala Glu His His Leu Ala Ala Leu Asp Ala Arg Cys Arg Glu Gln
        115
                            120
                                                125
Glu Glu Phe Gln Leu Ile Leu Asp Ala Val Arg Phe Cys Asn Tyr Leu
   130
Val Trp Phe Tyr Gln Ile Cys Tyr Ala Ile Tyr Ser Ser Ser Thr Phe
145
                    150
                                        155
Val Cys Ala Phe Leu Leu Gly Gln Pro Pro Tyr Ala Leu Tyr Leu Pro
                165
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Gly Leu Asp Trp Gln Arg Ser Gln Met Gln Phe Cys Ile Gln Ala Trp

Ile Glu Phe Leu Ile Met Asn Trp Thr Cys Leu His Gln Ala Ser Asp 195 200 205

Asp Val Tyr Ala Val Ile Tyr Leu Tyr Val Val Arg Ile Gln Val Gln 210 215 220

Leu Leu Ala Arg Arg Val Glu Lys Leu Gly Thr Asp Asp Ser Gly Gln 225 230 235

Val Glu Ile Tyr Pro Asp Glu Arg Arg Gln Glu Glu His Cys Ala Glu  $245 \hspace{1.5cm} 250 \hspace{1.5cm} 255$ 

Leu Gln Arg Cys Ile Val Asp His Gln Thr Met Leu Gln Leu Leu Asp \$260\$ \$265\$ \$270\$

Cys Ile Ser Pro Val Ile Ser Arg Thr Ile Phe Val Gln Phe Leu Ile \$275\$

Thr Ala Ala Ile Met Gly Thr Thr Met Ile Asn Ile Phe Ile Phe Ala 290 295 300

Asn Thr Asn Thr Lys Ile Ala Ser Ile Ile Tyr Leu Leu Ala Val Thr 305 \$310\$ \$315

Leu Gln Thr Ala Pro Cys Cys Tyr Gln Ala Thr Ser Leu Met Leu Asp \$325\$

Asn Glu Arg Leu Ala Leu Ala Ile Phe Gln Cys Gln Trp Leu Gly Gln \$340\$ \$350\$

Ser Ala Arg Phe Arg Lys Met Leu Leu Tyr Tyr Leu His Arg Ala Gln \$355\$ \$360\$ \$365

Gln Pro Ile Thr Leu Thr Ala Met Lys Leu Phe Pro Ile Asn Leu Ala 370 \$375\$

Thr Tyr Phe Ser Ile Ala Lys Phe Ser Phe Ser Leu Tyr Thr Leu Ile 385 \$390\$ \$395\$ 400

Lys Gly Met Asn Leu Gly Glu Arg Phe Asn Arg Thr Asn \$405\$

<210> 73

<211> 1089

<212> DNA

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	act Thr															144
	gtg Val 50															192
	acc Thr	-	-	-		-		-								240
	aaa Lys	-					_		-			-				288
_	tcc Ser			-	_		-				_		-		-	336
-	gtg Val	-	-		-				-	-			-	-		384
-	ttt Phe 130		-	-	-	-	-		-							432
	ccg Pro															480
	ttc Phe			_								-				528
	gcc Ala						-	-	_	_		-		_	-	576

	gtt Val				-	_	_		-		_	-		-		624
	ggc Gly 210															672
	aag Lys															720
-	ttg Leu	-		-				_	_	-	_					768
-	gtc Val	_					-					-	-	_	-	816
	cta Leu		_	-			-	-		_						864
	gcc Ala 290	_		-		-		_	_		-		_			912
_	gat Asp		_	-	_		_	-	_	_	-					960
	atg Met															1008
	cat His					_			_							1056
-	ttg Leu	_	-	_	_			_								1089

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Lys Trp Trp Arg Leu Trp Pro Arg Lys Glu Ser Val Ser Thr Pro Asp \$20\$

Trp Thr Asn Trp Gln Ala Tyr Ala Leu His Val Pro Phe Thr Phe Leu 35 40 45

Phe Val Leu Leu Leu Trp Leu Glu Ala Ile Lys Ser Arg Asp Ile Glu 50 \$55\$ 60

Gly Lys Val Ile Asn Ile Trp Lys Tyr Ala His Val Ala Gln Gly Ile \$85\$ 90 95

Leu Ser Glu Trp Ser Thr Trp Asp Leu Phe Glu Leu Arg Ser Lys Gln \$100\$

Glu Val Asp Met Trp Arg Phe Glu His Arg Arg Phe Asn Arg Val Phe \$115\$ \$120\$ \$125\$

Met Phe Tyr Cys Leu Cys Ser Ala Gly Val Ile Pro Phe Ile Val Ile 130 \$135\$

Gln Pro Leu Phe Asp Ile Pro Asn Arg Leu Pro Phe Trp Met Trp Thr 145 \$150\$

Pro Phe Asp Trp Gln Gln Pro Val Leu Leu Trp Tyr Ala Phe Ile Tyr 165 \$170\$

Gln Ala Thr Thr Ile Pro Ile Ala Cys Ala Cys Asn Val Thr Met Asp 180 185 190

Ala Val Asn Trp Tyr Leu Met Leu His Leu Ser Leu Cys Leu Arg Met

Leu Gly Gln Arg Leu Ser Lys Leu Gln His Asp Asp Lys Asp Leu Arg 210 215 220

Glu Lys Phe Leu Glu Leu Ile His Leu His Gln Arg Leu Lys Gln Gln 225 230 235 240

Ala	Leu	Ser	Ile	Glu 245	Ile	Phe	Ile	Ser	Lys 250	Ser	Thr	Phe	Thr	Gln 255	Ile	
Leu	Val	Ser	Ser 260	Leu	Ile	Ile	Cys	Phe 265	Thr	Ile	Tyr	Ser	Met 270	Gln	Met	
Tyr	Leu	Val 275	Ala	Met	Ile	Met	Gln 280	Val	Met	Leu	Pro	Thr 285	Ile	Tyr	Gly	
Asn	Ala 290	Val	Ile	Asp	Ser	Ala 295	Asn	Met	Leu	Thr	Asp 300	Ser	Met	Tyr	Asn	
Ser 305	Asp	Trp	Pro	Asp	Met 310	Asn	Cys	Arg	Met	Arg 315	Arg	Leu	Val	Leu	Met 320	
Phe	Met	Val	Tyr	Leu 325	Asn	Arg	Pro	Val	Thr 330	Leu	Lys	Ala	Gly	Gly 335	Phe	
Phe	His	Ile	Gly 340	Leu	Pro	Leu	Phe	Thr 345	Lys	Thr	Met	Asn	Gln 350	Ala	Tyr	
Ser	Leu	Leu 355	Ala	Leu	Leu	Leu	Asn 360	Met	Asn	Gln						
	> 75															
	L> 11															
	2> Di															
<213	5> DI	rosor	onila	i me.	Lano	jaste	er									
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	L> CI															
		L) ·		5)												
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1				5					10					15		
ttg	cgg	gtg	caa	att	ctc	gtt	tat	cgc	tgc	atg	ggc	atc	gat	ttg	tgg	96
Leu	Arg	Val	Gln 20	Ile	Leu	Val	Tyr	Arg 25	Cys	Met	Gly	Ile	Asp 30	Leu	Trp	
agc	ccc	acg	atg	gcg	aat	gac	cgc	ccg	tgg	ctg	acc	ttt	gtc	aca	atg	144
Ser	Pro	Thr	Met	Ala	Asn	Asp	Arg	Pro	Trp	Leu	Thr	Phe	Val	Thr	Met	

35 40 45

					atg Met 55								192
					ctg Leu				_				240
-	-	_		_	gtc Val			_		-		-	288
					atc Ile								336
					gat Asp								384
	-	-	_		agt Ser 135		_		-	-		-	432
-				-	ctg Leu	_							480
					att Ile								528
					gtg Val								576
					tat Tyr								624
					ttc Phe 215								672
					atc Ile								720

225 230 235 240

gag ctg gag gqg ctc qtc cag gtg ctg ctg ctg cac cag aag ggc ctc 768 Glu Leu Glu Gly Leu Val Gln Val Leu Leu His Gln Lys Gly Leu 245 250 255 cag atc gcc gat cac att gcg gac aag tac cqg ccg ctg atc ttt ttg Gln Ile Ala Asp His Ile Ala Asp Lys Tyr Arg Pro Leu Ile Phe Leu 260 265 cag ttc ttt ctg tcc gcc ttg cag atc tgc ttc att gga ttc cag gtg 864 Gln Phe Phe Leu Ser Ala Leu Gln Ile Cys Phe Ile Gly Phe Gln Val 275 280 285 get gat etg ttt eee aat eeg eag agt ete tae ttt ate gee ttt gtg Ala Asp Leu Phe Pro Asn Pro Gln Ser Leu Tvr Phe Ile Ala Phe Val 290 295 gge teg etg etc atc gea etg ttc atc tac teg aag tge gge gaa aat 960 Gly Ser Leu Leu Ile Ala Leu Phe Ile Tyr Ser Lys Cys Gly Glu Asn 305 310 atc aag agt gcc agc ctg gat ttc gga aac ggg ctg tac gag acc aac 1008 Ile Lvs Ser Ala Ser Leu Asp Phe Glv Asn Glv Leu Tvr Glu Thr Asn 325 330 335 tgg acc gac ttc tcg cca ccc act aaa aga gcc ctc ctc att gcc gcc 1056 Trp Thr Asp Phe Ser Pro Pro Thr Lys Arg Ala Leu Leu Ile Ala Ala 340 345 atg ege gee cag ega eet tge cag atg aag gge tac ttt tte gag gee 1104 Met Arg Ala Gln Arg Pro Cys Gln Met Lys Gly Tyr Phe Phe Glu Ala

355 360 365

agc atd gcc acc tte tcg acg att gtt cgc tct gcc gtg tcg tac atc 115

age atg gcc acc ttc tcg acg att gtt cgc tct gcc gtg tcg tac atc 1152 Ser Met Ala Thr Phe Ser Thr Ile Val Arg Ser Ala Val Ser Tyr Ile 370 375 380

atg atg ttg cgc tcc ttt aat gcc 1176 Met Met Leu Arg Ser Phe Asn Ala 385 390

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  1 10 15
- Leu Arg Val Gln Ile Leu Val Tyr Arg Cys Met Gly Ile Asp Leu Trp  $$20$ \ \, 25$ \ \, 30$
- Ser Pro Thr Met Ala Asn Asp Arg Pro Trp Leu Thr Phe Val Thr Met 35 40 45
- Gly Pro Leu Phe Leu Phe Met Val Pro Met Phe Leu Ala Ala His Glu 50 55 60
- Ala Ser Met Leu Thr Leu Val Lys Phe Leu Leu Phe Cys Tyr His Arg \$85\$ 90 95
- Lys Glu Phe Val Gly Leu Ile Tyr His Ile Arg Ala Ile Leu Ala Lys
- Glu Ile Glu Val Trp Pro Asp Ala Arg Glu Ile Ile Glu Val Glu Asn 115 120 125
- Gln Ser Asp Gln Met Leu Ser Leu Thr Tyr Thr Arg Cys Phe Gly Leu 130 135 140
- Ala Gly Ile Phe Ala Ala Leu Lys Pro Phe Val Gly Ile Ile Leu Ser 145 · 150 155 160
- Ser Ile Arg Gly Asp Glu Ile His Leu Glu Leu Pro His Asn Gly Val
- Tyr Pro Tyr Asp Leu Gln Val Val Met Phe Tyr Val Pro Thr Tyr Leu
- Trp Asn Val Met Ala Ser Tyr Ser Ala Val Thr Met Ala Leu Cys Val 195 200 205
- Asp Ser Leu Leu Phe Phe Phe Thr Tyr Asn Val Cys Ala Ile Phe Lys 210 215 220
- Ile Ala Lys His Arg Met Ile His Leu Pro Ala Val Gly Gly Lys Glu 225 230 235 240
- Glu Leu Glu Gly Leu Val Gln Val Leu Leu Leu His Gln Lys Gly Leu  $245 \hspace{1.5cm} 250 \hspace{1.5cm} 255$

Gln	Ile	Ala	Asp 260	His	Ile	Ala	Asp	Lys 265	Tyr	Arg	Pro	Leu	Ile 270	Phe	Leu	
Gln	Phe	Phe 275	Leu	Ser	Ala	Leu	Gln 280	Ile	Cys	Phe	Ile	Gly 285	Phe	Gln	Val	
Ala	Asp 290	Leu	Phe	Pro	Asn	Pro 295	Gln	Ser	Leu	Tyr	Phe 300	Ile	Ala	Phe	Val	
Gly 305	Ser	Leu	Leu	Ile	Ala 310	Leu	Phe	Ile	Tyr	Ser 315	Lys	Cys	Gly	Glu	Asn 320	
Ile	Lys	Ser	Ala	Ser 325	Leu	Asp	Phe	Gly	Asn 330	Gly	Leu	Tyr	Glu	Thr 335	Asn	
Trp	Thr	Asp	Phe 340	Ser	Pro	Pro	Thr	Lys 345	Arg	Ala	Leu	Leu	Ile 350	Ala	Ala	
Met	Arg	Ala 355	Gln	Arg	Pro	Cys	Gln 360	Met	Lys	Gly	Tyr	Phe 365	Phe	Glu	Ala	
Ser	Met 370	Ala	Thr	Phe	Ser	Thr 375	Ile	Val	Arg	Ser	Ala 380	Val	Ser	Tyr	Ile	
Met 385	Met	Leu	Arg	Ser	Phe 390	Asn	Ala									
<21:	0> 7 ⁻ L> 12 2> Di 3> Di	221 NA	ohila	a mel	Lanoç	jast∈	er									
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atg		aac			gaa Glu	-		-	-	_		-	-	-	-	48
					gct Ala		Lys		Tyr							96

												tat Tyr		144
						-		-			-	 gta Val		192
	_		-			-	-	-				 agc Ser	-	240
												aag Lys 95		288
												agg Arg		336
-			-		-	-		-	_	-		 gaa Glu		384
												gga Gly		432
				_		-		-				ccc Pro		480
												gcc Ala 175		528
_		_	_									gac Asp		576
												tat Tyr		624
		Cys			Ile		Gly					gtg Val		672

					cac His 230											720
					cat His											768
	_	_	_		cta Leu	-	-				-					816
	-	_	_		gag Glu	-					_	_				864
					ctg Leu											912
					tat Tyr 310											960
-	_			-	tat Tyr			-			-	_				1008
					gtg Val				-			-	-			1056
		-		-	ttc Phe	-								-	-	1104
	_	_		-	tgc Cys			-			-	_	-			1152
_			_	-	atc Ile 390				-	_		_			-	1200
-				-	tat Tyr											1221

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Asp Phe Leu Arg Leu Ala Val Lys Phe Tyr Asn Thr Leu Gly Ile Asp 20 25 30

Pro Tyr Glu Thr Gly Arg Lys Arg Thr Ile Trp Phe Gln Ile Tyr Phe 35 40 45

Ala Leu Asn Met Phe Asn Met Val Phe Ser Phe Tyr Ala Glu Val Ala 50 60

Thr Leu Val Asp Arg Leu Arg Asp Asn Glu Asn Phe Leu Glu Ser Cys 65 70 75 80

Ile Leu Leu Ser Tyr Val Ser Phe Val Val Met Gly Leu Ser Lys Ile 85 90 95

Gly Ala Val Met Lys Lys Lys Pro Lys Met Thr Ala Leu Val Arg Gln  $100 \hspace{1.5cm} 105 \hspace{1.5cm} 110 \hspace{1.5cm}$ 

Leu Glu Thr Cys Phe Pro Ser Pro Ser Ala Lys Val Gln Glu Glu Tyr 115 120 125

Ala Val Lys Ser Trp Leu Lys Arg Cys His Ile Tyr Thr Lys Gly Phe  $130\,$   $\,$   $\,$   $140\,$ 

Gly Gly Leu Phe Met Ile Met Tyr Phe Ala His Ala Leu Ile Pro Leu 145 \$150\$ 155 \$160

Phe Ile Tyr Phe Ile Gln Arg Val Leu Leu His Tyr Pro Asp Ala Lys 165 170 175

Gln Ile Met Pro Phe Tyr Gln Leu Glu Pro Trp Glu Phe Arg Asp Ser  $180 \,$   $\,$   $185 \,$   $\,$   $190 \,$ 

Trp Leu Phe Tyr Pro Ser Tyr Phe His Gln Ser Ser Ala Gly Tyr Thr 195 \$200\$

Ala Thr Cys Gly Ser Ile Ala Gly Asp Leu Met Ile Phe Ala Val Val

Leu Gln Val Ile Met His Tyr Glu Arg Leu Ala Lys Val Leu Arg Glu 225  $\phantom{\bigg|}$  230  $\phantom{\bigg|}$  235  $\phantom{\bigg|}$  240

Phe Lys Ile Gln Ala His Asn Ala Pro Asn Gly Ala Lys Glu Asp Ile \$245\$ \$250\$

Arg Lys Leu Gln Ser Leu Val Ala Asn His Ile Asp Ile Leu Arg Leu  $260 \hspace{1.5cm} 265 \hspace{1.5cm} 270 \hspace{1.5cm}$ 

Thr Asp Leu Met Asn Glu Val Phe Gly Ile Pro Leu Leu Leu Asn Phe 275 280 285

Ile Ala Ser Ala Leu Leu Val Cys Leu Val Gly Val Gln Leu Thr Ile  $290 \ \ 295 \ \ \ 300$ 

Ala Leu Ser Pro Glu Tyr Phe Cys Lys Gln Met Leu Phe Leu Ile Ser 305 310 315

Val Leu Leu Glu Val Tyr Leu Leu Cys Ser Phe Ser Gln Arg Leu Ile  $325 \hspace{1.5cm} 330 \hspace{1.5cm} 335$ 

Asp Ala Ser Glu Asn Val Gly His Ala Ala Tyr Asp Met Asp Trp Leu 340 345 350

Gly Ser Asp Lys Arg Phe Lys Lys Ile Leu Ile Phe Ile Ser Met Arg 355 360 365

Ser Gln Lys Pro Val Cys Leu Lys Ala Thr Val Val Leu Asp Leu Ser 370 375 380

Met Pro Thr Met Ser Ile Phe Leu Gly Met Ser Tyr Lys Phe Phe Cys 385  $\phantom{\bigg|}$  390  $\phantom{\bigg|}$  395  $\phantom{\bigg|}$  400

Ala Val Arg Thr Met Tyr Gln 405

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<211> 1212

<212> DNA

<213> Drosophila melanogaster

<220>

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<222> (1)..(1212)

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cga	ata	cca	gta	cad	ttt	tac	aga	aco	att	gga	gag	gat	atc	tac	acc	96
-			-	-			Arg	-				-			-	
			20					25		-		•	30	-		
	_		_				aaa	_				-				144
His	Arg		Thr	Asn	Pro	Leu	Lys	Ser	Leu	Leu	Phe	_	Ile	Tyr	Leu	
		35					40					45				
tat	aca	aga	ttc	ata	aat	ttt	aat	cta	tta	gta	atc	aat	gaa	cta	ata	192
		-					Asn	_	_	-			-	_		
	50					55					60					
							gac									240
	Phe	Tyr	Asn	Ser		Gln	Asp	Phe	Glu		Ile	Arg	Leu	Ala		
65					70					75					80	
aca	ata	act	cca	tat	atc	gga	ttt	tct	cta	att	act	gat	ttt	aaa	caa	288
		-		-			Phe		_	-	-	-				
				85					90					95		
-	-					_	aaa				_			-	-	336
Ala	Ala	Met		Arg	Gly	Lys	Lys	Thr 105	Leu	Ile	Met	Leu	Leu 110	Asp	Asp	
			100					105					110			
tta	gag	aac	ator	cat	cca	aaa	acc	ctq	qca	aaq	caa	atq	qaa	tac	aaa	384
_			-				Thr	_	-	_		-	-			
		115					120					125				
_		-			-		atg		-							432
Leu		Asp	Phe	GLu	Lys	Thr 135	Met	Lys	Arg	Val	11e	Asn	lle	Pne	Thr	
	130					133					140					
ttt	ctc	tac	ttq	qcc	tat	acq	act	acq	ttc	tcc	ttt	tat	ccg	gcc	atc	480
							Thr									
145		-			150					155					160	
_	-						ttc	_			-					528
ГЛS	Ala	Ser	Val		Phe	Asn	Phe	Leu		Tyr	Asp	Thr	Phe	Asp 175	Arg	
				165					170					1/3		

Asn	Phe	Gly	Phe 180	Leu	Ile	Trp	Phe	Pro 185	Phe	Asp	Ala	Thr	Arg 190	Asn	Asn	
-					-	tac Tyr		-		-			-			624
			-			tgc Cys 215	-	-		-		-	-	-		672
	_		_			ttt Phe					-	_			-	720
						gag Glu										768
			_			gac Asp										816
	_	_		_		tct Ser		-					_	-		864
						gcc Ala 295										912
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						Gly										1008
						aac Asn										1056
						ttg Leu										1104
tca	ata	aga	ccg	ccg	act	ttt	ccc	ccc	ata	tcc	ttg	gtt	acc	tat	atg	1152

Ser Ile Arg Pro Pro Thr Phe Pro Pro Ile Ser Leu Val Thr Tyr Met 370 375 aag gtc atc agc atg tog tat caa ttt ttt gcc tta ctt aga acc aca 1200 Lys Val Ile Ser Met Ser Tyr Gln Phe Phe Ala Leu Leu Arg Thr Thr 385 390 tac age aat aat 1212 Tyr Ser Asn Asn <210> 80 <211> 404 <212> PRT <213> Drosophila melanogaster <400> 80 Met Glu Thr Ala Lys Asp Asn Thr Ala Arg Thr Phe Met Glu Leu Met 5 10 Arg Val Pro Val Gln Phe Tyr Arg Thr Ile Gly Glu Asp Ile Tyr Ala 20 His Arg Ser Thr Asn Pro Leu Lys Ser Leu Leu Phe Lys Ile Tyr Leu 35 40 Tyr Ala Glv Phe Ile Asn Phe Asn Leu Leu Val Ile Gly Glu Leu Val 50 5.5 Phe Phe Tyr Asn Ser Ile Gln Asp Phe Glu Thr Ile Arg Leu Ala Ile Ala Val Ala Pro Cvs Ile Glv Phe Ser Leu Val Ala Asp Phe Lys Gln 85 90 Ala Ala Met Ile Arg Gly Lys Lys Thr Leu Ile Met Leu Leu Asp Asp Leu Glu Asn Met His Pro Lys Thr Leu Ala Lys Gln Met Glu Tyr Lys 115 120 Leu Pro Asp Phe Glu Lys Thr Met Lys Arg Val Ile Asn Ile Phe Thr 130 135 140 Phe Leu Cvs Leu Ala Tvr Thr Thr Thr Phe Ser Phe Tvr Pro Ala Ile

Lys Ala Ser Val Lys Phe Asn Phe Leu Gly Tyr Asp Thr Phe Asp Arg

165 170 175

Asn Phe Gly Phe Leu Ile Trp Phe Pro Phe Asp Ala Thr Arg Asn Asn  $180 \hspace{1cm} 185 \hspace{1cm} 190$ 

Leu Ile Tyr Trp Ile Met Tyr Trp Asp Ile Ala His Gly Ala Tyr Leu 195 200 . 205

Ala Gly Ile Ala Phe Leu Cys Ala Asp Leu Leu Leu Val Val Ile 210 \$215\$

Thr Gln Ile Cys Met His Phe Asn Tyr Ile Ser Met Arg Leu Glu Asp 225 230 235 240

His Pro Cys Asn Ser Asn Glu Asp Lys Glu Asn Ile Glu Phe Leu Ile  $245 \hspace{1.5cm} 250 \hspace{1.5cm} 255$ 

Gly Ile Ile Arg Tyr His Asp Lys Cys Leu Lys Leu Cys Glu His Val \$260\$

Asn Asp Leu Tyr Ser Phe Ser Leu Leu Leu Asn Phe Leu Met Ala Ser 275 280 285

Met Gln Ile Cys Phe Ile Ala Phe Gln Val Thr Glu Ser Thr Val Glu 290 295 300

Val Ile Ile Ile Tyr Cys Ile Phe Leu Met Thr Ser Met Val Gln Val 305 \$310\$ \$315

Phe Met Val Cys Tyr Tyr Gly Asp Thr Leu Ile Ala Ala Ser Leu Lys  $325 \hspace{1.5cm} 330 \hspace{1.5cm} 335$ 

Val Gly Asp Ala Ala Tyr Asn Gln Lys Trp Phe Gln Cys Ser Lys Ser 340 345 350

Tyr Cys Thr Met Leu Lys Leu Leu Ile Met Arg Ser Gln Lys Pro Ala 355 360 365

Ser Ile Arg Pro Pro Thr Phe Pro Pro Ile Ser Leu Val Thr Tyr Met  $370 \ \ 375 \ \ 380$ 

Lys Val Ile Ser Met Ser Tyr Gln Phe Phe Ala Leu Leu Arg Thr Thr 385 \$390\$ \$395\$

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	1				5					10					15		
	acg	gtg	ttc	tgg	atc	atg	ggc	tac	gac	atg	ctg	ggc	gtt	ccg	aag	acc	96
	Thr	Val	Phe	Trp	Ile	Met	Gly	Tyr	Asp	Met	Leu	Gly	Val	Pro	Lys	Thr	
				20					25					30			
	cgc	tct	cgc	agg	ata	cta	tac	tgg	ata	tat	cgt	ttc	ctc	tgt	ctc	gcc	144
	Arg	Ser	Arg	Arg	Ile	Leu	Tyr	Trp	Ile	Tyr	Arg	Phe	Leu	Cys	Leu	Ala	
			35					40					45				
	agc	cat	ggg	gtc	tgt	gta	gga	gtc	atg	gta	ttt	cgt	atg	gtg	gag	gca	192
	Ser	His	Gly	Val	Cys	Val	Gly	Val	Met	Val	Phe	Arg	Met	Val	Glu	Ala	
		50					55					60					
	aag	acc	att	gac	aat	gtt	tcg	ctg	atc	atg	cgg	tat	gcc	act	ctg	gtc	240
	Lys	Thr	Ile	Asp	Asn	Val	Ser	Leu	Ile	Met	Arg	Tyr	Ala	Thr	Leu	Val	
	65					70					75					80	
	acc	tat	atc	atc	aac	tcg	gat	acg	aaa	ttc	gca	act	gtc	tta	caa	agg	288
	Thr	Tyr	Ile	Ile	Asn	Ser	Asp	Thr	Lys	Phe	Ala	Thr	Val	Leu	Gln	Arg	
					85					90					95		
	agt	gca	att	caa	agt	cta	aac	tca	aaa	ctg	gcc	gaa	cta	tat	ccg	aag	336
	Ser	Ala	Ile	Gln	Ser	Leu	Asn	Ser	Lys	Leu	Ala	Glu	Leu	Tyr	Pro	Lys	
				100					105					110			
	acc	acg	ctg	gac	agg	atc	tat	cac	cgg	gtg	aat	gat	cac	tat	tgg	acc	384
	Thr	Thr	Leu	Asp	Arg	Ile	Tyr	His	Arg	Val	Asn	Asp	His	Tyr	Trp	Thr	
			115					120					125				
	aaσ	tca	ttt	gta	tat	tta	qtt	att	atc	tac	att	ggt	tca	tca	att	atg	432
		Ser															
	-	130					135			-		140					

				att Ile 150								480
				atg Met								528
				tgg Trp			-		-			576
				atg Met								624
				gtg Val								672
-		_	 -	cac His 230	_	-		-	-	-	 -	720
				aaa Lys								768
				aat Asn							-	816
				geg Ala								864
				ttg Leu								912
				gtc Val 310								960
	-	_	 	cgc Arg		 -		-			-	1008

ttt cac gat get tet ata geg tac aag agg tac etg etc ata ate att 1056 Phe His Asp Ala Ser Ile Ala Tyr Lys Arg Tyr Leu Leu Ile Ile Ile ate agg geg cag cag cee gtg gaa ctt aat gec atg ggc tae etg tee Ile Arg Ala Gln Gln Pro Val Glu Leu Asn Ala Met Gly Tyr Leu Ser 355 360 365 att tog etg gae ace ttt aaa cag etg atg age gte tee tae egg gtt 1152 Ile Ser Leu Asp Thr Phe Lys Gln Leu Met Ser Val Ser Tyr Arg Val 370 375 ata acc atg ctc atg cag atg att cag 1179 Ile Thr Met Leu Met Gln Met Ile Gln 385 390 <210> 82 <211> 393 <212> PRT <213> Drosophila melanogaster <400> 82 Met Glu Pro Val Gln Tyr Ser Tyr Glu Asp Phe Ala Arg Leu Pro Thr 1 Thr Val Phe Trp Ile Met Gly Tyr Asp Met Leu Gly Val Pro Lys Thr 20 25 Arg Ser Arg Arg Ile Leu Tyr Trp Ile Tyr Arg Phe Leu Cys Leu Ala 40 Ser His Gly Val Cys Val Gly Val Met Val Phe Arg Met Val Glu Ala 50 55 Lys Thr Ile Asp Asn Val Ser Leu Ile Met Arg Tyr Ala Thr Leu Val 70 75 80 65 Thr Tyr Ile Ile Asn Ser Asp Thr Lys Phe Ala Thr Val Leu Gln Arg 85 Ser Ala Ile Gln Ser Leu Asn Ser Lys Leu Ala Glu Leu Tyr Pro Lys 105 110 100 Thr Thr Leu Asp Arg Ile Tyr His Arg Val Asn Asp His Tyr Trp Thr 115 120

Lys Ser Phe Val Tyr Leu Val Ile Ile Tyr Ile Gly Ser Ser Ile Met

130 135 140

Val Val Ile Gly Pro Ile Ile Thr Ser Ile Ile Ala Tyr Phe Thr His 145 150 155 160

Asn Val Phe Thr Tyr Met His Cys Tyr Pro Tyr Phe Leu Tyr Asp Pro  $165 \\ 170 \\ 175$ 

Glu Lys Asp Pro Val Trp Ile Tyr Ile Ser Ile Tyr Ala Leu Glu Trp 180 \$180\$

Leu His Ser Thr Gln Met Val Ile Ser Asn Ile Gly Ala Asp Ile Trp \$195\$ 200 205

Leu Leu Tyr Phe Gln Val Gln Ile Asn Leu His Phe Arg Gly Ile Ile 210 \$215\$

Arg Ser Leu Ala Asp His Lys Pro Ser Val Lys His Asp Gln Glu Asp 225 230 230

Arg Lys Phe Ile Ala Lys Ile Val Asp Lys Gln Val His Leu Val Ser  $245 \hspace{1.5cm} 250 \hspace{1.5cm} 255 \hspace{1.5cm}$ 

Leu Gln Asn Asp Leu Asn Gly Ile Phe Gly Lys Ser Leu Leu Ser 260 265 270

Leu Leu Thr Thr Ala Ala Val Ile Cys Thr Val Ala Val Tyr Thr Leu 275 280 285

Ile Gln Gly Pro Thr Leu Glu Gly Phe Thr Tyr Val Ile Phe Ile Gly  $290 \hspace{1.5cm} 295 \hspace{1.5cm} 300 \hspace{1.5cm}$ 

Thr Ser Val Met Gln Val Tyr Leu Val Cys Tyr Tyr Gly Gln Gln Val 305  $$\rm 310$$  315 320

Leu Asp Leu Val Glu Arg Glu Val Ala His Ala Val Tyr Asn His Asp \$325\$

Phe His Asp Ala Ser Ile Ala Tyr Lys Arg Tyr Leu Leu Ile Ile Ile 340 345 350

Ile Arg Ala Gln Gln Pro Val Glu Leu Asn Ala Met Gly Tyr Leu Ser \$355\$ \$360\$ \$365

Ile Ser Leu Asp Thr Phe Lys Gln Leu Met Ser Val Ser Tyr Arg Val 370 \$375\$

Ile Thr Met Leu Met Gln Met Ile Gln

	)> 83 .> 11															
	.> II															
			hi1-	a mel	2000	ra ata										
-21-	,, 01	.0301	)111 I C	ı meı	ano	yası	31									
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	)> 83															
				tac												48
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1				5					10					15		
gga	ttc	gat.	ccc	agt	act	cca	caa	cta	agt	cta	aaa	cat	ccc	atc	taa	96
				Ser												
-		•	20					25			-		30		-	
gcc	ggg	att	ctc	atc	ctg	tcc	ttg	atc	tct	cac	aac	tgg	ccc	atg	gta	144
Ala	Gly		Leu	Ile	Leu	Ser		Ile	Ser	His	Asn		Pro	Met	Val	
		35					40					45				
~+ ~		~~~	ata	caq	ant	at a	+	a. a	++ ~	200	aat	at a	200	a.a	220	192
		-	_	Gln	-			-	_		_	_	_	-		132
val	50	niu	пси	GIII	1100	55	561	riop	пси	1111	60	пса	1111	пор	7.011	
ttt	gcg	gtg	ttt	atg	caa	gga	tca	cag	agc	acc	ttc	aag	ttc	ctg	gtc	240
Phe	Ala	Val	Phe	Met	Gln	Gly	Ser	Gln	Ser	Thr	Phe	Lys	Phe	Leu	Val	
65					70					75					80	
				cga		-			_	_			-	-		288
Met	Met	Ата	ьys	Arg 85	Arg	Arg	TIE	GTĀ	90	Leu	ire	nıs	Arg	95	HIS	
				0.5					90					93		
aaœ	cta	aac	caq	gcg	acc	aσt	acc	acq	ccc	aat	cac	cta	gag	aaq	atc	336
-			_	Ala	-											
-			100					105					110			
		-		caa												384
Glu	Arg		Asn	Gln	Leu	Asp	_	Tyr	Val	Ala	Arg		Phe	Arg	Asn	
		115					120					125				
acc	acc	tac	aga	ata	att	tat	acc	tea	acc	ata	aca	ccc	ato	tta	ctt	432

Ala	Ala 130	Tyr	Gly	Val	Ile	Cys 135	Ala	Ser	Ala	Ile	Ala 140	Pro	Met	Leu	Leu	
					gtg Val 150											480
					tgg Trp	_	-		-	_						528
					ggc Gly											576
-		-	_	-	acc Thr					_						624
					ctg Leu											672
		-		-	ctg Leu 230				-		-				-	720
_	-	_	-	_	gaa Glu											768
			_		agt Ser		_			-	_	_	-		-	816
		_	-		tgg Trp	-	-	-				_	-			864
		-			atc Ile		_									912
		-	-		agt Ser 310	_	-		-		-	-				960
atc	aat	tgg	cca	gaa	atg	acg	cca	aag	aaa	aga	aga	ctc	tgg	caa	atg	1008

Ile Asn Trp Pro Glu Met Thr Pro Lys Lys Arg Arg Leu Trp Gln Met 325 330 qtq atc atq aqq qcq caq cqa ccq qct aaq att ttt qqa ttc atq ttc Val Ile Met Arg Ala Gln Arg Pro Ala Lys Ile Phe Gly Phe Met Phe gtt gtg gac ttg cca ctg ctg ctt tgg gtc atc aga act gcg ggc tca Val Val Asp Leu Pro Leu Leu Leu Trp Val Ile Arg Thr Ala Gly Ser 355 360 365 ttt ctg gcc atg ctt agg act ttc gag cgt 1134 Phe Leu Ala Met Leu Arg Thr Phe Glu Arg 370 375 <210> 84 <211> 378 <212> PRT <213> Drosophila melanogaster <400> 84 Met Asp Ala Ser Tvr Phe Ala Val Gln Arg Arg Ala Leu Glu Ile Val 5 15 1 10 Gly Phe Asp Pro Ser Thr Pro Gln Leu Ser Leu Lys His Pro Ile Trp 20 25 Ala Gly Ile Leu Ile Leu Ser Leu Ile Ser His Asn Trp Pro Met Val 35 40 Val Tyr Ala Leu Gln Asp Leu Ser Asp Leu Thr Arg Leu Thr Asp Asn 55 Phe Ala Val Phe Met Gln Gly Ser Gln Ser Thr Phe Lys Phe Leu Val 70 75 Met Met Ala Lys Arg Arg Ile Gly Ser Leu Ile His Arg Leu His 85 90 Lys Leu Asn Gln Ala Ala Ser Ala Thr Pro Asn His Leu Glu Lys Ile 100 105 110 Glu Arq Glu Asn Gln Leu Asp Arq Tyr Val Ala Arg Ser Phe Arg Asn

120 Ala Ala Tyr Gly Val Ile Cys Ala Ser Ala Ile Ala Pro Met Leu Leu 140 130 135

125

- Gly Leu Trp Gly Tyr Val Glu Thr Gly Val Phe Thr Pro Thr Thr Pro 145 \$150\$
- Met Glu Phe Asn Phe Trp Leu Asp Glu Arg Lys Pro His Phe Tyr Trp \$165\$ \$170\$ \$175\$
- Pro Ile Tyr Val Trp Gly Val Leu Gly Val Ala Ala Ala Ala Trp Leu 180 185 190
- Ala Ile Ala Thr Asp Thr Leu Phe Ser Trp Leu Thr His Asn Val Val
  195 200 205
- Ile Gln Phe Gln Leu Leu Glu Leu Val Leu Glu Glu Lys Asp Leu Asn 210 \$215\$
- Gly Gly Asp Ser Arg Leu Thr Gly Phe Val Ser Arg His Arg Ile Ala 225  $\phantom{\bigg|}$  230  $\phantom{\bigg|}$  235  $\phantom{\bigg|}$  240
- Leu Asp Leu Ala Lys Glu Leu Ser Ser Ile Phe Gly Glu Ile Val Phe  $245 \\ \hspace*{1.5cm} 250 \\ \hspace*{1.5cm} 255 \\ \hspace*{1.5cm}$
- Val Lys Tyr Met Leu Ser Tyr Leu Gln Leu Cys Met Leu Ala Phe Arg \$260\$
- Phe Ser Arg Ser Gly Trp Ser Ala Gln Val Pro Phe Arg Ala Thr Phe 275 280 285
- Leu Val Ala Ile Ile Ile Gln Leu Ser Ser Tyr Cys Tyr Gly Gly Glu 290 295 300
- Tyr Ile Lys Gln Gln Ser Leu Ala Ile Ala Gln Ala Val Tyr Gly Gln 305 \$310\$ 315 \$320
- Ile Asn Trp Pro Glu Met Thr Pro Lys Lys Arg Arg Leu Trp Gln Met 325 330 335
- Val Ile Met Arg Ala Gln Arg Pro Ala Lys Ile Phe Gly Phe Met Phe  $340 \hspace{1.5cm} 345 \hspace{1.5cm} 350 \hspace{1.5cm}$
- Val Val Asp Leu Pro Leu Leu Trp Val Ile Arg Thr Ala Gly Ser \$355\$ \$360\$
- Phe Leu Ala Met Leu Arg Thr Phe Glu Arg 370 375

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<222	> CE > (1	.)(	1065													
atg		aaa	cta Leu													48
_		_	acc Thr 20				-									96
			ctg Leu													144
			gag Glu	-		_		_								192
			gga Gly													240
			ttg Leu													288
			cta Leu 100													336
			caa Gln													384
			acg Thr													432
gtc	atg	gca	ctg	gaa	ccc	ctc	gtt	cag	tcg	tgc	att	atc	cag	ttc	ata	480

Val 145	Met	Ala	Leu	Glu	Pro 150	Leu	Val	Gln	Ser	Cys 155	Ile	Ile	Gln	Phe	Ile 160	
				ctg Leu 165												528
				cac His												576
				gaa Glu		-			-	-						624
		_	_	cat His												672
	-			ctc Leu		-	-			-					-	720
		-	-	atg Met 245												768
				tat Tyr	_	-										816
				tca Ser												864
	_		-	gcc Ala			-				-			_	-	912
			-	ata Ile				_	-	_	-		-		_	960
				agg Arg 325												1008
ata	ttg	atg	acc	atc	aca	tac	aga	ttt	ttc	gcg	gtt	ata	cga	caa	act	1056

Ile Leu Met Thr Ile Thr Tyr Arg Phe Phe Ala Val Ile Arg Gln Thr \$340\$ \$345 \$350

gta gaa aag Val Glu Lys 355 1065

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<211> 355

<212> PRT

<213> Drosophila melanogaster

<400> 86

Met Glu Lys Leu Arg Ser Tyr Glu Asp Phe Ile Phe Met Ala Asn Met 1  $\phantom{\bigg|}$  5  $\phantom{\bigg|}$  10  $\phantom{\bigg|}$  15

Met Phe Lys Thr Leu Gly Tyr Asp Leu Phe His Thr Pro Lys Pro Trp \$20\$ \$25\$ \$30

Trp Arg Tyr Leu Leu Val Arg Gly Tyr Phe Val Leu Cys Thr Ile Ser 35 40 45

Asn Phe Tyr Glu Ala Ser Met Val Thr Thr Arg Ile Ile Glu Trp Glu 50 55 60

Ser Leu Ala Gly Ser Pro Ser Lys Ile Met Arg Gln Gly Leu His Phe 65 70 75 80

Phe Tyr Met Leu Ser Ser Gln Leu Lys Phe Ile Thr Phe Met Ile Asn 85 90 95

Arg Lys Arg Leu Leu Gln Leu Ser His Arg Leu Lys Glu Leu Tyr Pro \$100\$ \$105\$ \$110\$

His Lys Glu Gln Asn Gln Arg Lys Tyr Glu Val Asn Lys Tyr Tyr Leu 115 120 125

Ser Cys Ser Thr Arg Asn Val Leu Tyr Val Tyr Tyr Phe Val Met Val 130 135 140

Val Met Ala Leu Glu Pro Leu Val Gln Ser Cys Ile Ile Gln Phe Ile 145 150 150 155

Val Asn Val Ser Leu Gly Thr Asp Leu Trp Met Met Cys Val Ser Ser 165 170 175

Gln Ile Ser Met His Leu Gly Tyr Leu Ala Asn Met Leu Ala Ser Ile

180 185 190

Arg Pro Ser Pro Glu Thr Glu Gln Gln Asp Cys Asp Phe Leu Ala Ser 195 200 205

Ile Ile Lys Arg His Gln Leu Met Ile Arg Leu Gln Lys Asp Val Asn 210  $$\rm 215$$ 

Tyr Val Phe Gly Leu Leu Leu Ala Ser Asn Leu Phe Thr Thr Ser Cys 225  $\phantom{\bigg|}$  230  $\phantom{\bigg|}$  235  $\phantom{\bigg|}$  240

Leu Leu Cys Cys Met Ala Tyr Tyr Thr Val Val Glu Gly Phe Asn Trp \$245\$

Glu Gly Ile Ser Tyr Met Met Leu Phe Ala Ser Val Ala Ala Gln Phe  $260 \\ 265 \\ 270$ 

Tyr Val Val Ser Ser His Gly Gln Met Leu Ile Asp Leu Ser Thr Asn 275 \$280\$

Leu Ala Lys Ala Ala Phe Glu Ser Lys Trp Tyr Glu Gly Ser Leu Arg 290 295 300

Tyr Lys Lys Glu Ile Leu Ile Leu Met Ala Gln Ala Gln Arg Pro Leu 305 \$310\$ 315 320

Glu Ile Ser Ala Arg Gly Val Ile Ile Ile Ser Leu Asp Thr Phe Lys \$325\$ \$330\$ \$335

Val Glu Lys 355

<210> 87 <211> 1272

<212> DNA

<213> Drosophila melanogaster

<220>

<221> CDS

<222> (1)..(1272)

<223> DORLU 22.1

<400> 87

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	gga Gly							_	-	-			-			96
	cgc Arg			-	-			_		-	-				-	144
	att Ile 50															192
-	tca Ser		-		-			-				-	-			240
	ctt Leu						_	-		_					_	288
	tat Tyr	-	-	_		_	-				-	-	-	-	_	336
	gtg Val															384
-	tac Tyr 130	-			-	-			_	-	-	-	-			432
	tcc Ser															480
	cat His															528
	aga Arg		-		-	_				-		_	-	_		576

					tat Tyr											624
					tgt Cys											672
					ttc Phe 230	-		-				_	-			720
-	-	-			aaa Lys							_				768
					tgt Cys											816
					tgc Cys											864
					ctg Leu						_					912
		-	-		acg Thr 310	-	-	-	-		_					960
-		-		_	agc Ser			_		-	-				-	1008
-					agc Ser				_	_	_	-		-	_	1056
	-	-			aaa Lys		-	-	-	_	-	-	_			1104
		-			ttc Phe			-				_			-	1152

atc cct ggc cta gct ttc cgg gct ttc att att cag tgg ttc agt cgt 1200 Ile Pro Gly Leu Ala Phe Arg Ala Phe Ile Ile Gln Trp Phe Ser Arg 385 390 395 tog ggt ttg ttt aac toe gga aat att tae aat tat get tta age egg 1248 Ser Gly Leu Phe Asn Ser Gly Asn Ile Tyr Asn Tyr Ala Leu Ser Arg 405 410 tgt tgt tac agc cag ttg gct aat 1272 Cys Cys Tyr Ser Gln Leu Ala Asn 420 <210> 88 <211> 424 <212> PRT <213> Drosophila melanogaster <400> 88 Met Leu Thr Asp Lys Phe Leu Arg Leu Gln Ser Ala Leu Phe Arg Leu Leu Gly Leu Glu Leu His Glu Gln Asp Val Gly His Arg Tyr Pro 20 -25 Trp Arg Ser Ile Cys Cys Ile Leu Ser Val Ala Ser Phe Met Pro Leu 35 Thr Ile Ala Phe Gly Leu Gln Asn Val Gln Asn Val Glu Gln Leu Thr 50 55 60 Asp Ser Leu Cys Ser Val Leu Val Asp Leu Leu Ala Leu Cys Lys Ile 65 70 75 Gly Leu Phe Leu Trp Leu Tyr Lys Asp Phe Lys Phe Leu Ile Gly Gln 85 90 Phe Tyr Cys Val Leu Gln Thr Glu Thr His Thr Ala Val Ala Glu Met 100 105 Ile Val Thr Arg Glu Ser Arg Arg Asp Gln Phe Ile Ser Ala Met Tyr 115 120 125 Ala Tyr Cys Phe Ile Thr Ala Gly Leu Ser Ala Cys Leu Met Ser Pro 130 135 140 Leu Ser Met Leu Ile Ser Tyr His Glu Gln Val Asn Cys Ser Arg Asn 145 150 155

- Phe His Phe Pro Val Cys Lys Lys Lys Tyr Cys Leu Ile Ser Arg Ile  $165 \hspace{1.5cm} 170 \hspace{1.5cm} 175$
- Leu Arg Tyr Ser Phe Cys Arg Tyr Pro Trp Asp Asn Met Lys Leu Ser 180 185 190
- Asn Tyr Ile Ile Ser Tyr Phe Trp Asn Val Cys Ala Ala Leu Gly Val
- Ala Leu Pro Thr Val Cys Val Asp Thr Leu Phe Cys Ser Leu Ser His 210 215 220
- Asn Leu Cys Ala Leu Phe Gln Ile Ala Arg His Lys Met Met His Phe 225 230 235 240
- Glu Gly Arg Asn Thr Lys Glu Thr His Glu Asn Leu Lys His Val Phe 245 250 255
- Gln Leu Tyr Ala Leu Cys Leu Asn Leu Gly His Phe Leu Asn Glu Tyr 260 265 270
- Phe Arg Pro Leu Ile Cys Gln Phe Val Ala Ala Ser Leu His Leu Cys 275 280 285
- Val Leu Cys Tyr Gln Leu Ser Ala Asn Ile Leu Gln Pro Ala Leu Leu 290 295 300
- Phe Tyr Ala Ala Phe Thr Ala Ala Val Val Gly Gln Val Ser Ile Tyr 305 310 315 320
- Cys Phe Cys Gly Ser Ser Ile His Ser Glu Cys Gln Leu Phe Gly Gln 325 330 335
- Ala Ile Tyr Glu Ser Ser Trp Pro His Leu Leu Gln Glu Asn Leu Gln 340 \$340\$
- Leu Val Ser Ser Leu Lys Ile Ala Met Met Arg Ser Ser Leu Gly Cys 355 360 365
- Pro Ile Asp Gly Tyr Phe Phe Glu Ala Asn Arg Glu Thr Leu Ile Thr  $370 \hspace{1cm} 375 \hspace{1cm} 380$
- Ile Pro Gly Leu Ala Phe Arg Ala Phe Ile Ile Gln Trp Phe Ser Arg 385 390 395 400
- Ser Gly Leu Phe Asn Ser Gly Asn Ile Tyr Asn Tyr Ala Leu Ser Arg \$405\$

## Cys Cys Tyr Ser Gln Leu Ala Asn 420

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<222	D> L> CI 2> (1 3> DO	L)													
atg	tca Ser	aag				-							-	-	48
	acc Thr		-	-	_		_	-	_	_		-			96
	gtt Val	-			_				-		-	-	-		144
-	ttt Phe 50			-			_	-							192
	atc Ile														240
	tcg Ser														288
	gac Asp				-										336
-	ggt Gly				-										384

	att Ile 130												432
	cca Pro												480
	cct Pro												528
	cat His												576
	ttt Phe												624
	tta Leu 210	 	-			-	_						672
	ata Ile		-						-				720
	att Ile												768
	tat Tyr												816
	ctc Leu												864
	aac Asn 290	-		_				_	-	-		-	912
_	tgc Cys				 -	-	-	-	-	_	 -		960

Arg Ph	tcc Ser														1008
cct aa. Pro Ly:															1056
gaa ac Glu Th															1104
gtt tge Val Try 370	Ile														1152
ctc tac Leu Tyr 385	-			-	-										1176
<210> ! <211> !															
<212> 1	- IXI														
<212> 1 <213> 1		phila	a mel	Lano	gaste	er									
	roso	phila	a mel	lano	gaste	er									
<213> 1	)roso) 90						Leu	Gly 10	Asn	Leu	Trp	Thr	Gln 15	Arg	
<213> 1 <400> 3 Met Se	oroso) 90 Lys	Leu	Ile 5	Glu	Val	Phe		10					15		
<213> 1 <400> 9 Met Ses 1	Oroson 90 Lys Phe	Leu Ala 20	Ile 5 Arg	Glu Met	Val Gly	Phe Leu	Asp 25	10 Leu	Gln	Pro	Asp	Lys 30	15 Lys	Gly	
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- Val Gly Thr Glu Trp Arg Ser Gln Asn Gln Arg Gly Gln Leu Met Ala Ala Ile Tyr Phe Met Met Cys Ala Gly Thr Ser Val Ser Phe Leu Leu Met Pro Val Ala Leu Thr Met Leu Lys Tyr His Ser Thr Gly Glu Phe Ala Pro Val Ser Ser Phe Arg Val Leu Leu Pro Tyr Asp Val Thr Gln Pro His Val Tyr Ala Met Asp Cys Cys Leu Met Val Phe Val Leu Ser Phe Phe Cys Cys Ser Thr Thr Gly Val Asp Thr Leu Tyr Gly Trp Cys Ala Leu Gly Val Ser Leu Gln Tyr Arg Arg Leu Gly Gln Gln Leu Lys Arg Ile Pro Ser Cys Phe Asn Pro Ser Arg Ser Asp Phe Gly Leu Ser Gly Ile Phe Val Glu His Ala Arg Leu Leu Lys Ile Val Gln His Phe Asn Tyr Ser Phe Met Glu Ile Ala Phe Val Glu Val Val Ile Ile Cys Gly Leu Tyr Cys Ser Val Ile Cys Gln Tyr Ile Met Pro His Thr Asn Gln Asn Phe Ala Phe Leu Gly Phe Phe Ser Leu Val Val Thr Thr Gln Leu Cys Ile Tyr Leu Phe Gly Ala Glu Gln Val Arg Leu Glu Ala Glu Arg Phe Ser Arg Leu Leu Tyr Glu Val Ile Pro Trp Gln Asn Leu Pro
- Pro Lys His Arg Lys Leu Phe Leu Phe Pro Ile Glu Arg Ala Gln Arg 340 345 350

Glu Thr Val Leu Gly Ala Tyr Phe Phe Glu Leu Gly Arg Pro Leu Leu 355 \$360\$

Val Trp Ile Phe Arg Thr Ala Gly Ser Phe Thr Thr Leu Met Asn Ala 370 375 Leu Tyr Ala Lys Tyr Glu Thr His 385 390 <210> 91 <211> 1359 <212> DNA <213> Drosophila melanogaster <220> <221> CDS <222> (1)..(1359) <223> DORLU 25.1 <400> 91 atg aag agc aca ttc aag gaa gaa agg att aag gac gac tcc aag cgt Met Lys Ser Thr Phe Lys Glu Glu Arg Ile Lys Asp Asp Ser Lys Arg ege gae etg ttt gta tte gtg agg caa ace atg tgt ata geg gee atg Arg Asp Leu Phe Val Phe Val Arg Gln Thr Met Cys Ile Ala Ala Met 20 tat ccc ttc ggt tac tac gtg aat gga tct gga gtc ctg gcc gtt ctg 144 Tyr Pro Phe Gly Tyr Tyr Val Asn Gly Ser Gly Val Leu Ala Val Leu 40 gtg cga ttc tgt gac ttg acc tac gag ctc ttt aac tac ttc gtt tcg 192 Val Arg Phe Cys Asp Leu Thr Tyr Glu Leu Phe Asn Tyr Phe Val Ser 50 55 gta cac ata gct ggc ctg tac atc tgc acc atc tac atc aac tat ggg Val His Ile Ala Gly Leu Tyr Ile Cys Thr Ile Tyr Ile Asn Tyr Gly 65 70 caa ggc gat ttg gac ttc ttc gtg aac tgt ttg ata caa acc att att

caa ggc gat ttg gac ttc ttc gtg aac tgt ttg ata caa acc att att 288 Gln Gly Asp Leu Asp Phe Phe Val Asn Cys Leu Ile Gln Thr Ile Ile 85 90 95

tat ctg tgg aca ata gcg atg aaa ctc tac ttt cgg agg ttc aga cct 336
Tyr Leu Trp Thr Ile Ala Met Lys Leu Tyr Phe Arg Arg Phe Arg Pro
100

 _	_		acc Thr		_			-			384
			gga Gly								432
			tgg Trp								480
			ctg Leu 165	-			-		-	 -	528
	-	_	tgg Trp			-				 -	576
			ctt Leu								624
			tcc Ser								672
			gat Asp								720
			ctt Leu 245								768
			tct Ser								816
			gag Glu								864
			tcc Ser								912

		cat His														960
		ccc Pro														1008
		gta Val														1056
		atg Met 355														1104
		atc Ile														1152
		ggt Gly					-	-			_	-		-	-	1200
-	-	cgc Arg	-	-		_			_	_			_		-	1248
		ctt Leu	_					-					-	-		1296
-		act Thr 435										_	-		_	1344
	-	gca Ala	-													1359
<211 <211	0> 92 1> 45 2> PE 3> Da	53	ohila	a mel	Lanoq	gaste	er									

 $<\!400\!>92$  Met Lys Ser Thr Phe Lys Glu Glu Arg Ile Lys Asp Asp Ser Lys Arg

	Val 65	His	Ile	Ala	Gly	Leu 70	Т
	Gln	Gly	Asp	Leu	Asp 85	Phe	P
12	Tyr	Leu	Trp	Thr 100	Ile	Ala	М
10	Gly	Leu	Leu 115	Asn	Thr	Ile	L
	Arg	Ser 130	Ala	Val	Gly	Phe	S 1
	Met 145	Ser	Lys	Leu	Trp	Ile 150	L
	Thr	Ile	Phe	Trp	Leu 165	Ala	L
losi.	Pro	Leu	Ala	Cys 180	Trp	Tyr	P
	Glu	Val	Val 195	Phe	Leu	Leu	G
	Ser	Phe 210	Ala	Ser	Ser	Ser	G 2
			1				

1				5					10					15	
Arg	Asp	Leu	Phe 20	Val	Phe	Val	Arg	Gln 25	Thr	Met	Суз	Ile	Ala 30	Ala	Met
Tyr	Pro	Phe 35	Gly	Tyr	Tyr	Val	Asn 40	Gly	Ser	Gly	Val	Leu 45	Ala	Val	Leu
Val	Arg 50	Phe	Cys	Asp	Leu	Thr 55	Tyr	Glu	Leu	Phe	Asn 60	Tyr	Phe	Val	Ser
Val 65	His	Ile	Ala	Gly	Leu 70	Tyr	Ile	Cys	Thr	Ile 75	Tyr	Ile	Asn	Tyr	Gly 80
Gln	Gly	Asp	Leu	Asp 85	Phe	Phe	Val	Asn	Cys 90	Leu	Ile	Gln	Thr	Ile 95	Ile
Tyr	Leu	Trp	Thr 100	Ile	Ala	Met	Lys	Leu 105	Tyr	Phe	Arg	Arg	Phe 110	Arg	Pro
Gly	Leu	Leu 115	Asn	Thr	Ile	Leu	Ser 120	Asn	Ile	Asn	Asp	Glu 125	Tyr	Glu	Thr
Arg	Ser 130	Ala	Val	Gly	Phe	Ser 135	Phe	Val	Thr	Met	Ala 140	Gly	Ser	Tyr	Arg
Met 145	Ser	Lys	Leu	Trp	Ile 150	Lys	Thr	Tyr	Val	Tyr 155	Суз	Cys	Tyr	Ile	Gly 160
Thr	Ile	Phe	Trp	Leu 165	Ala	Leu	Pro	Ile	Ala 170	Tyr	Arg	Asp	Arg	Ser 175	Leu
Pro	Leu	Ala	Cys 180	Trp	Tyr	Pro	Phe	Asp 185	Tyr	Thr	Gln	Pro	Gly 190	Val	Tyr
G1u	Val	Val 195	Phe	Leu	Leu	Gln	Ala 200	Met	Gly	Gln	Ile	Gln 205	Val	Ala	Ala
Ser	Phe 210	Ala	Ser	Ser	Ser	Gly 215	Leu	His	Met	Val	Leu 220	Cys	Val	Leu	Ile
Ser 225	Gly	Gln	Tyr	Asp	Val 230	Leu	Phe	Cys	Ser	Leu 235	Lys	Asn	Val	Leu	Ala 240
Ser	Ser	Tyr	Val	Leu 245	Met	Gly	Ala	Asn	Met 250	Thr	Glu	Leu	Asn	Gln 255	Leu
Gln	Ala	Glu	Gln	Ser	Ala	Ala	Asp	Val	Glu	Pro	Gly	Gln	Tyr	Ala	Tyr

Ser Val Glu Glu Glu Thr Pro Leu Gln Glu Leu Leu Lys Val Gly Ser 275 280 285

Ser Met Asp Phe Ser Ser Ala Phe Arg Leu Ser Phe Val Arg Cys Ile 290 295 300

Gln His His Arg Tyr Ile Val Ala Ala Leu Lys Lys Ile Glu Ser Phe 305 310 315 320

Tyr Ser Pro Ile Trp Phe Val Lys Ile Gly Glu Val Thr Phe Leu Met \$325\$

Cys Leu Val Ala Phe Val Ser Thr Lys Ser Thr Ala Ala Asn Ser Phe \$340\$ \$350\$

Met Arg Met Val Ser Leu Gly Gln Tyr Leu Leu Leu Val Leu Tyr Glu \$355\$

Leu Phe Ile Ile Cys Tyr Phe Ala Asp Ile Val Phe Gln Asn Ser Gln 370 375 380

Arg Cys Gly Glu Ala Leu Trp Arg Ser Pro Trp Gln Arg His Leu Lys 385 390 395 400

Asp Val Arg Ser Asp Tyr Met Phe Phe Met Leu Asn Ser Arg Arg Gln \$405\$ \$410\$

Phe Gln Leu Thr Ala Gly Lys Ile Ser Asn Leu Asn Val Asp Arg Phe 420 425 430

Arg Gly Thr Ile Thr Thr Ala Phe Ser Phe Leu Thr Leu Leu Gln Lys \$435\$

Met Asp Ala Arg Glu 450

<210> 93

<211> 1296

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<213> Drosophila melanogaster

<220>

<221> CDS

<222> (1)..(1296)

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- cag gat gtc gtc cac ata gtt ata tcc atc atg tcc gag tgg tta cgc 96 Gln Asp Val Val His Ile Val Ile Ser Ile Met Ser Glu Trp Leu Arg 20 25 30
- ttt ctg aaa cgc gat caa cag ctg gat gtg tac ttt ttt gca gtg ccc  $\phantom{0}$  144 Phe Leu Lys Arg Asp Gln Gln Leu Asp Val Tyr Phe Phe Ala Val Pro  $\phantom{0}$  35  $\phantom{0}$  40  $\phantom{0}$  45
- cgc ttg agt tta gac ata atg ggc tat tgg ccg ggc aaa act ggt gat  $\,$  192 Arg Leu Ser Leu Asp Ile Met Gly Tyr Trp Pro Gly Lys Thr Gly Asp  $\,$  50  $\,$  55
- aca tgg ccc tgg aga tcc ctg att cac ttc gca atc ctg gcc att ggc 240 Thr Trp Pro Trp Arg Ser Leu Ile His Phe Ala Ile Leu Ala Ile Gly 65 70 80
- gtg gcc acc gaa ctg cat gct ggc atg tgt ttt cta gac cga cag cag cag 288
  Val Ala Thr Glu Leu His Ala Gly Met Cys Phe Leu Asp Arg Gln Gln
  85
  90
  95
- att acc ttg gca ctg gag acc ctc tgt cca gct ggc aca tcg gcg gtc 336 Ile Thr Leu Ala Leu Glu Thr Leu Cys Pro Ala Gly Thr Ser Ala Val 100 105
- acg ctg ctc aag atg ttc cta atg ctg cgc ttt cgt cag gat ctc tcc 384
  Thr Leu Leu Lys Met Phe Leu Met Leu Arg Phe Arg Gln Asp Leu Ser
  115 120
- att atg tgg aac cgc ctg agg ggc ctg ctc ttc gat ccc aac tgg gag 432 Ile Met Trp Asn Arg Leu Arg Gly Leu Leu Phe Asp Pro Asn Trp Glu 130 140
- cga ccc gag cag cgg gac atc cgg cta aag cac tcg gcc atg gcg gct 480 Arg Pro Glu Gln Arg Asp Ile Arg Leu Lys His Ser Ala Met Ala Ala 145 150 160
- cgc atc aat ttc tgg ccc ctg tca gcc gga ttc ttc aca tgc acc acc 528
  Arg Ile Asn Phe Trp Pro Leu Ser Ala Gly Phe Phe Thr Cys Thr Thr
  165 170 175
- tac aac cta aag ccg ata ctg atc gca atg ata ttg tat ctc cag aat 570

Tyr	Asn	Leu	Lys 180	Pro	Ile	Leu	Ile	Ala 185	Met	Ile	Leu	Tyr	Leu 190	Gln	Asn	
						tgg Trp								_		624
	-	_				cca Pro 215				-						672
						acc Thr							-	-		720
					_	gcc Ala				-			-			768
_				-		atg Met		-				-		_	-	816
						tac Tyr										864
						atc Ile 295										912
						ctg Leu										960
			-	_	-	aat Asn		_		_						1008
						gcc Ala		-	-	-	-	-	-		_	1056
_	-		-			gga Gly		_		-	-	_	-			1104
ctg	tgc	cga	gcc	atg	ttc	tcc	tgt	ccg	tgg	cag	ctt	ttt	aag	cct	aaa	1152

Leu Cys Arg Ala Met Phe Ser Cys Pro Trp Gln Leu Phe Lys Pro Lys 370 375 380 caa cgt cga ctc gtt cag ctt ttg att ctc aga tcg cag cgt cct gtt 1200 Gln Arg Arg Leu Val Gln Leu Leu Ile Leu Arg Ser Gln Arg Pro Val 385 390 395 tcc atg gca gtg cca ttc ttt tcg cca tcg ttg gct acc ttt gct gcg 1248 Ser Met Ala Val Pro Phe Phe Ser Pro Ser Leu Ala Thr Phe Ala Ala 405 410 att ctt caa act tog ggt toc ata att geg etg gtt aag toe ttt cag Ile Leu Gln Thr Ser Gly Ser Ile Ile Ala Leu Val Lys Ser Phe Gln 420 430 <210> 94 <211> 432 <212> PRT <213> Drosophila melanogaster <400> 94 Met Lys Val Gly Phe Ala Thr Ile Gly Tyr Ile Lys Ser Ile Pro Cys 5 1.0 15 Gln Asp Val Val His Ile Val Ile Ser Ile Met Ser Glu Trp Leu Arg 25 20 30 Phe Leu Lys Arg Asp Gln Gln Leu Asp Val Tyr Phe Phe Ala Val Pro Arg Leu Ser Leu Asp Ile Met Gly Tyr Trp Pro Gly Lys Thr Gly Asp 55 Thr Trp Pro Trp Arg Ser Leu Ile His Phe Ala Ile Leu Ala Ile Gly 70 75 Val Ala Thr Glu Leu His Ala Gly Met Cys Phe Leu Asp Arg Gln Gln Ile Thr Leu Ala Leu Glu Thr Leu Cys Pro Ala Gly Thr Ser Ala Val 100 105 110 Thr Leu Leu Lys Met Phe Leu Met Leu Arg Phe Arg Gln Asp Leu Ser 115 125

135

Ile Met Trp Asn Arg Leu Arg Gly Leu Leu Phe Asp Pro Asn Trp Glu

Arg 145	Pro	Glu	Gln	Arg	Asp 150	Ile	Arg	Leu	Lys	His 155	Ser	Ala	Met	Ala	Ala 160
Arg	Ile	Asn	Phe	Trp 165	Pro	Leu	Ser	Ala	Gly 170	Phe	Phe	Thr	Cys	Thr 175	Thr
Tyr	Asn	Leu	Lys 180	Pro	Ile	Leu	Ile	Ala 185	Met	Ile	Leu	Tyr	Leu 190	Gln	Asn
Arg	Tyr	Glu 195	Asp	Phe	Val	Trp	Phe 200	Thr	Pro	Phe	Asn	Met 205	Thr	Met	Pro
Lys	Val 210	Leu	Leu	Asn	Tyr	Pro 215	Phe	Phe	Pro	Leu	Thr 220	Tyr	Ile	Phe	Ile
Ala 225	Tyr	Thr	Gly	Tyr	Val 230	Thr	Ile	Phe	Met	Phe 235	Gly	Gly	Cys	Asp	Gly 240
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Ile			-								_			624
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- Tyr Leu Phe Gln Ser Tyr Phe Ala Val Tyr Cys Leu Thr Trp Leu Leu  $165 \hspace{1.5cm} 170 \hspace{1.5cm} 175$
- Ile Glu Val Leu Cys Leu Glu Leu Arg Gln Ile His Arg His Asn Tyr 195 200 205
- Gly Leu Gln Glu Leu Arg Met Glu Thr Asn Arg Leu Val Lys Leu His  $210 \ \ 215 \ \ 220 \ \$
- Gln Lys Ile Met Gly Val Asn Phe Ser Leu Val Ser Leu Ser Val Leu 225  $\phantom{\bigg|}$  230  $\phantom{\bigg|}$  235  $\phantom{\bigg|}$  240
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- Gly Asp Gln Leu Ser Gln Lys Ser Leu Gln Ile Ser Glu Ala Ala Tyr 275 280 285
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- Cys Val Ile Ile Arg Arg Gly Gln Asp Pro Leu Ile Met Arg Ala Ser  $305 \hspace{1cm} 310 \hspace{1cm} 315 \hspace{1cm} 320$
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Tyr Val Asp Ile Tyr Leu Ser Thr Glu Ser Leu Asp Phe Ile Ile Arg 50 55 60

Asn Val Tyr Leu Ala Val Leu Phe Thr Asn Thr Val Val Arg Gly Val 65 70 75 80

Leu Leu Cys Val Gln Arg Phe Ser Tyr Glu Arg Phe Ile Asn Ile Leu  $85 \hspace{1.5cm} 90 \hspace{1.5cm} 95$ 

Lys Ser Phe Tyr Ile Glu Leu Leu Gln Ser Asp Asp Pro Ile Ile Asn  $100 \hspace{1.5cm} 105 \hspace{1.5cm} 105 \hspace{1.5cm} 110$ 

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Ile Phe Gly Ser Glu Arg Val Leu Pro Tyr Gly Met Tyr Leu Pro Thr 145 \$150\$

Ile Asp Glu Tyr Lys Tyr Ala Ser Pro Tyr Tyr Glu Ile Phe Phe Val

Ile Gln Ala Ile Met Ala Pro Met Gly Cys Cys Met Tyr Ile Pro Tyr 180 \$180\$

a consider a second contract of the

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Val Leu Gln His Lys Leu Arg Ser Leu Glu Lys Leu Lys Asn Glu Gln 210 215 220

Val Arg Gly Glu Ile Ile Trp Cys Ile Lys Tyr Gln Leu Lys Leu Ser 225  $\phantom{\bigg|}$  230  $\phantom{\bigg|}$  235  $\phantom{\bigg|}$  240

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Lys Tyr Gly Ile Leu Gln Ser Phe Asp Ile Ala Ile Ala Ala Tyr Glu \$325\$ \$330\$ \$335

Ser Asn Trp Met Asp Phe Asp Val Asp Thr Gln Lys Thr Leu Lys Phe \$340\$ \$345\$

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1354

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